Docket No.: 204372000300
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Lynn E. SPITLER et al.

Application No.: 08/105,444

Filed: August 11, 1993 Art Unit: 1644

For: PROSTATIC CANCER VACCINE Examiner: P. Gambel

APPELLANT'S BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants hereby appeal from the final rejection of claims 1-14 and 21-40 mailed June 11, 2003. A Notice of Appeal was filed along with a Petition for an Extension of Time on November 10, 2003 and was received in the Office on November 12, 2003. The Brief was due on January 12, 2004. A petition for an extension of time of one month until February 12, 2004 is attached hereto, along with the required fee. Appellants respectfully request that the rejection be reversed. In accordance with 37 C.F.R. § 1.192, this Brief is filed in triplicate and is accompanied by the required fee.

Enclosed herewith is the following Exhibit:

Exhibit A: Terminal Disclaimers

I. REAL PARTY IN INTEREST

The present application is assigned to Jenner Technologies, a California Corporation, which was purchased by Immuno-Designed Molecules, a French Corporation.

II. RELATED APPEALS AND INTERFERENCES

There is a pending appeal in the related case, Application Serial No. 09/300,978, which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 34 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 15-20

2. Claims withdrawn from consideration but not canceled: None

3. Claims pending: 1-14, 21-40

4. Claims allowed: None

5. Claims rejected: 1-14, 21-40

C. Claims On Appeal

The claims on appeal are claims 1-14 and 21-40.

IV. STATUS OF AMENDMENTS

Applicant filed an Amendment After Final Rejection on August 11, 2003. The Examiner responded to the Amendment After Final Rejection in an Advisory Action mailed October 3, 2003.

The Amendment After Final Rejection did not contain amendments to the claims. Accordingly, the claims enclosed herein as Appendix A are as of the response filed by the Applicant on March 3, 2003.

V. SUMMARY OF INVENTION

Prior art formulations for vaccines elicit an antitumor response from the host immune system using antigens that are uniquely or largely associated with the malignant or metastatic nature of the tumor cell *per se*. The present invention represents a different approach in that, rather than using antigens associated with a metastatic or malignant phenotype, the present invention employs antigens that over represented or substantially uniquely expressed on normal tissue, namely prostate tissue. *See* Specification, at page 9, line 29 to page 10, line 2. In other words, these antigens are not uniquely associated with the malignant or metastatic nature of the tumor cell, but rather are found on both normal and malignant prostate tissue. *See* Specification, at page 4, lines 11-22. Thus, the invention takes advantage of the fact of the non-essential nature of the prostate organ, and elicits an antitumor immune response that simultaneously eliminates normal and malignant prostate tissue. *See* Specification, at page 4, lines 11-22.

While the prior art recognizes that prostate specific antigen (PSA) can be used in healthy experimental animals to generate antibodies for use in diagnosis, there is no suggestion that PSA or any other antigen over represented on normal prostate tissue can be used to elicit a protective or therapeutic immune response against prostate cancer. According to the prior art, the use of antigens highly expressed on normal and malignant tissues is undesirable because (1) the elicitation of an immune response directed to such an antigen results in the destruction of normal and malignant tissue, a potentially fatal consequence for the successful elimination of a tumor, and (2) elicitation of an immune response to an antigen highly expressed on normal tissue, or a self-antigen, is difficult due to the host immune system's anergy or tolerance to such self-antigens.

Prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), and prostatic acid phosphatase (PAP) are three representative species of the genus of over represented antigens specifically expressed in normal prostate tissue that are useful in the present invention. *See* Specification, at page 7, line 12 to page 10, line 2. The antigens of the present invention can be supplied, for example, as the antigen *per se* or as an expression system which is able to produce the protein or immunologically effective peptide *in situ* in the subject. *See* Specification, at page 10, line 3 to page 12, line 19. The invention is directed to methods of use and pharmaceutical vaccine compositions. *See* Specification, at page 13, line 16 to page 15, line 17.

Thus, the invention of claims 1-3 is directed to methods of eliciting an effective antitumor immune response to prostate tumors in a subject bearing or potentially bearing a prostate tumor using antigens that are overexpressed on normal prostate tissue, such as PSA, PSMA, and PAP. Claims 5-8 further defines the method as being directed to a subject afflicted with prostate cancer and/or wherein the tumor of the subjects has been surgically excised, but is still at risk for recurrence. The invention of claims 9-14 and 21-40 is directed to pharmaceutical or veterinary compositions for eliciting an effective antitumor immune response to prostate tumors in a subject bearing or potentially bearing a prostate tumor using antigens that are overexpressed on normal prostate tissue. One or more of the prostate antigens can be delivered as a protein or immunologically effective portion thereof or an expression system that produces such a protein or immunologically effective portion thereof. Claims 10-13, 24-27, 30-33, and 37-40 are directed to the same composition where either the antigen is further encapsulated in a liposome or coupled to a liposome and/or the liposome contains an adjuvant.

VI. ISSUES

The following issues are presented for review:

1. Whether the instant specification sufficiently describes the "antigen over represented in the prostate gland or an immunologically effective portion thereof," "nucleic acid that generates said antigen or antigens in situ", "proteins", or "peptides" of the claimed methods and compositions in a manner that reasonably conveys possession of the subject matter to the skilled artisan, as reflected in the rejection of claims 1-14 and 21-40 under 35 U.S.C. § 112, first paragraph.

2. Whether the instant specification reasonably enables any "over represented prostate specific antigen", any "immunologically effective portion thereof", "protein", or "peptide" as reflected in the rejection of claims 1-14 and 21-40 under 35 U.S.C. § 112, first paragraph.

3. Whether the claims particularly point out and distinctly claim the subject matter that Appellant regards as the invention as reflected in the rejection of claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40 under 35 U.S.C. § 112, second paragraph.

4. Whether the claims are obvious under 35 U.S.C. § 103 (a) over the combination of Spitler (U.S. Patent 5,783,867) in view of Israeli *et al.* (U.S. Patent 5,538,866), Horoszewicz (U.S. Patent 5,162,504), Andriole *et al.* (*Ann. Rev. Med.* 42: 9-15 (1991)) and in view of the art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley *et al.* (*Sem. Surg. Oncol.* 5: 293-301 (1989)).

5. Whether the claims are unpatentable under the judicially-created doctrine of obviousness-type double patenting over claims 1-8 of U.S. Patent No. 5,925,362 and over claims 13, 15, 16, and 18-24 of co-pending Application Serial No. 09/300,978.

VII. GROUPING OF CLAIMS

The inventive concept of the claims lies in the following groups: Group 1 (claims 1-7) drawn to methods of inducing an antitumor response using over represented prostate antigens, and

Group II (claims 8-14 and 21-40) drawn to vaccine compositions comprising over represented prostate antigens. While Applicants maintain that the claimed inventions of both groups of claims are patentable, the case law seems to suggest differing standards in assessing the patentability of method and composition claims. Thus, for the purposes of the rejections under 35 U.S.C. §§ 112, first paragraph and 103 (a), as set forth in Issues 1, 2, and 4, the claims in Group I and II should be considered separately. It should be evident that the rejection under 35 U.S.C. § 112, second paragraph, as set forth in Issue 3 above, is applicable to claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40. Issue 3 relates to whether the claims particularly point out and distinctly claim over represented antigens. All claims may be considered together for the purposes of the rejection under the judicially created doctrine of obviousness-type double patenting as set forth in Issue 5.

VIII. ARGUMENTS

It is believed that all issues should be resolved in favor of Appellants for the following reasons:

Issue 1: Claims 1-14 and 21-40 are sufficiently described in the instant specification to reasonably convey to the skilled artisan possession of the over represented antigens in the prostate gland or an immunologically effective portion thereof, nucleic acids that generate these antigens as well as proteins and peptides of over represented antigens at the time of filing.

Claims 1-14 and 21-40 were rejected as lacking sufficient written description in the specification to reasonably convey to a person of skill in the art possession of the claimed methods and compositions at the time of filing. *See* Paper No. 33, pages 2-5. According to the Action, the disclosure of whole PSA, PSMA, and PAP and the accompanying disclosure of relevant, identifying characteristics of the genus is insufficient to fully describe the genus of over represented prostate antigens, immunologically effective portions thereof, nucleic acids that generate these antigens, and the associated proteins and peptides useful in the claimed methods and compositions. Appellants assert this rejection is in error.

A. Legal standard of the written description requirement

The written description requirement prevents an applicant from later asserting that he invented which he did not. *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cir. 1991). In other words, the "description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented [or had possession of] what is claimed." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). Possession of the invention can be shown by actual reduction to practice or showing that the invention was ready for patenting through the description of sufficiently distinguishing characteristics. *See Pfaff v. Wells Electronics, Inc.*, 48 U.S.P.Q.2d 1641, 1647 (1998) (emphasis added). The adequacy of the description is measured by the understanding of one of ordinary skill in the art. *Id.* Therefore, the fulfillment of the written description requirement is a fact-based inquiry that necessarily varies depending on the nature of the invention. *Enzo Biochem v. Gen-Probe, Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002).

The written description requirement for a genus requires only a sufficient description of a genus of a representative number of species by actual reduction to practice, reduction to drawing, or by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus to one of skill in the art. *Manual of Patent Examination Procedure* (hereinafter "MPEP") § 2163(II)(A)(3)(a)(ii) (8th Ed. 2001). A representative number of species is that number that adequately represents the genus and is an inverse function of the skill and knowledge in the art. *Id.* Thus, the description must be such that the person of skill in the art recognizes that the inventor was in possession of the necessary common attributes or features of the elements possessed by members of the genus, providing a measure of predictability for the utility described for the genus. *Id.* (emphasis added).

B. <u>The specification sufficiently discloses of the genus of over represented antigens and immunologically effective portions thereof to the person of skill in the art</u>.

The disclosure clearly allows one of skill in the art to recognize that Appellants had possession of the invention at the time of filing through (1) the disclosure of the necessary common attribute or feature of the antigens used in the claimed methods of Group I and compositions of Group II, and (2) the disclosure of three representative genus members, namely PSA, PSMA, and PAP, and thus fulfills the written description requirement under 35 U.S.C. § 112, first paragraph.

Appellants respectfully submit that the specification as filed sufficiently discloses the necessary common attribute or feature of the antigens uses in the claimed methods and compositions. *See Pfaff v. Wells Electronics, Inc.*, 48 U.S.P.Q.2d 1641, 1647 (1998) (holding that possession of the invention can be shown by actual reduction to practice or showing that the invention was ready for patenting through the description of sufficiently distinguishing characteristics). First and foremost, Appellants explicitly identify the necessary common attribute of these antigens - they are over represented on normal prostate tissue while also being expressed on malignant prostate tissue. More specifically, the specification discloses that the antigen useful in the claimed invention is one that is over represented or substantially uniquely present on prostate gland so that prostate derived tissue can be distinguished from other tissue by virtue of the presence of these antigens. *See* specification at page 9, line 29 - page 10, line 2. The specification further discloses that the concentration or representation of this antigen is sufficiently higher in normal prostate tissue relative to other normal tissues so that "the prostate can be effectively targeted by the immune response raised against this antigen with relative sparring of other organs or tissues." *See* specification at page 5, lines 15-24. One of skill in the art would readily recognize that such an antigen is expressed almost exclusively, *i.e.*, substantially uniquely, on normal prostate tissue at such a level that an immune response elicited against that antigen results in the simultaneous elimination of normal and malignant prostate tissue. Second, the specification further describes the genus of useful antigens through the disclosure of three representative antigens: PSA, PSMA, and PAP. Each of these antigens is a protein and is substantially uniquely expressed or over represented on normal prostate tissue such that the antigen expression profile distinguished the prostate tissue from other tissues. *See* specification at page 7, line 13 to page 9, line 21. Moreover, this expression

profile is recognized in the prior art. *See, e.g.*, Peterson, *The Urinary Tract and Male Reproductive System* IN 17 PATHOLOGY 928 (Rubin and Farber, eds. 1988) (stating that "[b]oth prostate-specific antigen [PSA] and prostatic acid phosphatase [PAP] are found by immunohistochemical techniques in normal ... and neoplastic prostatic glandular epithelium"); Israeli et al., *Cancer Res.* 53(3):227-30 (1993) (stating that "the [PSMA] antigen is expressed exclusively by normal and neoplastic prostate cells and metastases"). Therefore, the disclosure in the specification clearly identifies the antigens for use in the present claims to the person of skill in the art.

Moreover, Appellants submit that the standard applied to the claims of Group I by the Examiner appears to be one that would be applicable to claims drawn to novel over represented antigens *per se*. However, such is not the appropriate standard for the instant claims. In fact, the courts have repeatedly held that for claims drawn to the use of known compounds in a manner auxiliary to the invention, the written description must only be so specific as to lead the skilled artisan to that class of compounds.

The Federal Circuit's predecessor court, the Court of Customs and Patent Appeals, repeatedly recognized a standard for claims drawn to known compounds used in a manner auxiliary to the claimed methods distinct from that applied to claims drawn to novel compositions *per se*, a standard that has not been disturbed by the Federal Circuit. For example, in *In re Fuetterer*, the court examined claims drawn to a rubber stock composition useful in producing tire treads with a limitation of including "an organic salt" capable of maintaining an homogeneous distribution of another component in the composition. 138 U.S.P.Q. 217 (C.C.P.A. 1963). The specification disclosed the function desired and four members of the genus having the recited function. The court held that the disclosure fulfilled the written description requirement because there is "nothing in patent law which requires appellant to discover which of all those salts have such a property and which will function properly in the combination." *Id.* at 223. The court then specifically recognized that such claims did not exclude additional organic salts discovered in the future with the cited properties, saying

> If others in the future discover what organic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some organic salt not named by appellant in his disclosure.

Id. (emphasis added).

Likewise, in *In re Herschler*, the court held that claims drawn to the use of a mixture of DMSO with a physiologically active steroidal agent in a therapeutic method was sufficiently described by a generic definition and a single disclosed example. 200 U.S.P.Q. 211 (C.C.P.A. 1979). In the application at issue in *Herschler*, the court sought to determine whether an earlier filed application qualified as a proper priority document for claims to physiologically active steroidal agents. In the earliest filed application, steroidal agents were not disclosed *in haec verba.* This application provided a single example using a corticosteroid with DMSO and a definition of the term "physiologically active substance." *Id.* at 716-717 (defining the term as "any substance which has a demonstrable and desired physiological activity in the sense that animal tissue responds thereto"). The court held that

> claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one of ordinary skill in the art to that class of compounds.

Id. at 718 (emphasis added). The court reasoned that the functional description of the compounds useful in the claimed methods and compositions was sufficient description since the claims were not drawn to novel steroidal agents. *Id.* at 717. As in *In re Fuetterer*, the court recognized that the compounds useful in the DMSO method was much broader than the diversity of compound disclosed in the application, but nonetheless held that "one having ordinary skill in the art would have found the use of the subgenus of steroids to be apparent from the written description [provided]." *Id.* Thus, the class of compounds useful in the claimed methods and compositions necessarily included any future identified compounds with the identified characteristic, *i.e.*, being physiologically active.

The claims of the instant application are analogous to those of *In re Fuetterer* and *In re Herschler*. The patentability of the instant invention lies not in the identification of novel prostate antigens, immunologically effective portions thereof, or prostate proteins or peptides, rather in knowing what to do with the prostate antigens that have the disclosed physical and functional characteristics. Alternatively stated, the specific identity of the prostate antigens used is auxiliary to the invention of the claimed methods and compositions beyond the necessary common attribute disclosed. Because the specification clearly leads the skilled artisan to this class of antigens through

the specific, necessary physical and functional characteristics and the disclosed examples, the instant written description is sufficient. Likewise, the compositions of Group II are sufficiently identified by their common necessary attribute.

Because the specification clearly leads the skilled artisan to this class of antigens through the specific, necessary physical and functional characteristics and the disclosed examples, the instant specification is sufficient for the claims of Groups I and II.

C. Neither *Fiers*, *Fiddes*, nor *Eli Lilly* are applicable to the instant invention.

Fiers, *Fiddes*, and *Eli Lilly* are distinct from the instant invention because the claimed invention in each of theses cases is a novel DNA sequence. While conception and reduction to practice of a novel DNA sequence may require the identification of the actual DNA sequence being claimed, it does not follow that the requirement for the recitation of DNA sequence is applicable to claims involving a method using proteins and DNA sequences where the patentability of the method lies in the method itself, not in a particular protein or DNA sequence. All functional descriptions of genetic material do not fail as a matter of law. *Amgen, Inc. v. Hoeschst Marion Roussel, Inc.*, 65 U.S.P.Q.2d 1385, 1398 (Fed. Cir. 2003). Rather the court looks to the knowledge in the art and whether the terms are such that an ordinary skilled artisan would comprehend the invention. For reasons articulated *infra*, Appellants submit that the skilled artisan would recognize the Appellants had possession of what is claimed, particularly for the invention of the claims in Groups I. Therefore, the requirement for a specific DNA sequence by the courts in *Fiers*, *Fiddes*, and *Eli Lilly* does not apply to the instant methods.

For the reasons stated above, the written description rejection under 35 U.S.C. § 112, first paragraph may be properly withdrawn.

Issue 2: The specification provides sufficient guidance for one of skill in the art to make and use the methods and compositions of claims 1-14 and 21-40.

Claims 1-14 and 21-40 were rejected as failing to meet the enablement requirement. *See* Paper No. 33, pages 5-10. According to the Action, Applicants have not provided sufficient enabling disclosure regarding (1) any over represented prostate specific antigen, (2)

immunologically effective portions of over represented prostate specific antigens, or (3) protein or peptides of these antigens. Appellants assert this rejection is in error.

A. Legal standard of the enablement requirement.

Enablement under 35 U.S.C. § 112, first paragraph requires that the specification of a patent teach one of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright,* 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993). Undue experimentation is determined by a series of factual inquiries that can include the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). While working examples are one consideration in the analysis, compliance with the enablement requirement does not turn on whether a working example is disclosed. MPEP § 2164.02. In fact, a lack of evidence that the invention works as claimed, standing alone, is an insufficient reason to reject a claimed invention on lack of enablement. *Id.*

Thus, the specification must be enabling to one of skill in the art. MPEP § 2164.05(b). Thus, the amount of guidance or direction required to fulfill the enablement requirement is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 91, 94 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 947 (1987) (holding that a specification need not disclose what is well known in the art).

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art ... would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could use the genus as a whole without undue experimentation.

MPEP §2164.02.

B. The specification supports the breadth of the claimed invention.

The specification reasonably enables the use of the genus of over represented antigens, immunologically effective portions thereof, encoding nucleic acids, and proteins and peptides in the claimed methods and compositions. The specification provides adequate guidance as to the identity of the antigens useful in the claimed methods and compositions. The specification provides three representative examples in the genus of over represented antigens, *i.e.*, PSA, PSMA, and PAP as well as an explicit, specific definition for the genus. Antigens in this genus are those that are substantially uniquely present on the prostate gland so that prostate derived tissue can be distinguished from other tissue by virtue of the presence of these antigens and that can serve as a target for an immune response with relative sparring of other organs or tissues. *See* Specification at page 9, line 29 - page 10, line 2 and page 5, lines 15-24. Moreover, each of the antigens disclosed is a protein. One of skill in the art would recognize these antigens as host antigens, *i.e.*, expressed on normal tissue, whose expression level is a distinguishing feature of prostate tissue and therefore allows a targeted immune response to eliminate the prostate tissue (normal and malignant) with relative sparring of other tissues.

Appellants respectfully submit that further biochemical information on members of the genus of over represented antigens useful in the claimed methods and compositions is not required for the reasonable enablement of the methods and compositions because the antigens are not defined by biochemical properties, but rather by level of expression on normal prostate tissue. Identifying biochemical information is not required. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63, U.S.P.Q.2d 1609, 1613 (2002). It is only necessary that the antigens be described in a way that permits the person of skill in the art to identify the class of antigens useful in the methods and compositions. The antigens are sufficiently identified as antigens substantially uniquely expressed on prostate tissue to inform the skilled artisan of their identity. To date, the Examiner has provided no scientific explanation or scientific publication to support his allegation that the physical/functional characteristics provided by the specification are insufficient for the skilled artisan making and using the claimed invention.

Second, the specification teaches the skilled artisan how to make, formulate, and administer full-length antigens, immunologically reactive portions thereof, and nucleic acids

encoding one or more of those antigens *in situ*. On page 10, line 9 to page 12, line 2, the specification teaches the skilled artisan how to prepare antigens. On page 12, lines 3-23, the specification teaches the skilled artisan how to generate immunologically effective portions of the antigens. Examples of generating the antigens *in situ* by an expression system are set forth on page 6, line 21 to page 7, line 14. On page 16, line 24 to page 17, line 4, the specification provides an example of a viral expression vector for the claimed nucleic acids, as well as disclosing "naked" DNA as useful in the claimed methods and compositions as well as a description of compositions by which the claimed antigens may be formulated on page 14, line 15 to page 17, line 4. Furthermore, the specification on page 17, line 5 to page 19, line 20 provides the skilled artisan with a description of how to administer antigens and encoding nucleic acids of the claimed methods and compositions.

Any experimentation that is required to practice the claimed methods is routine. The specification teaches all of the steps required for practicing the proven claimed invention, and all that remains is repetition of these teachings to practice the scope of the claims. In particular, Applicants submit that the patentability of the claimed methods of Group I lies in knowing what to do with the antigens, not in the identification of novel proteins or immunogenic peptides. Moreover, post-filing evidence of record demonstrates that the claimed methods have been carried out according to the teachings of the specification using PSA as an antigen and result in an effective antitumor immune response. Repeating vaccine studies for different antigens, including full-length polypeptides, portions of those polypeptides, and nucleic acids that express the foregoing polypeptides *in situ*, is routine. The routine nature of identifying and using immunogenic peptide is confirmed by each of the experts in the declarations of record. *See* Declaration of Phillip O. Livingston, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996; Declaration of Jean Claude Bystryn, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996, Declaration of Michael Mastrangelo, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996, and Declaration of Robert Oldham, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996. To date, the Examiner has provided no evidence to the contrary nor has there been any indication as to why the declarations of these experts are according no weight. In sum, the claimed inventions of Groups I and II can be easily practiced by a person of ordinary skill in the art without undue experimentation in view of the disclosure in the specification and the knowledge in the art.

C. **The evidence of record definitively demonstrates the operability of the claimed inventions using the guidance provided in the specification.**

The specification as filed provides all the guidance necessary for making and using over represented prostate antigens as tumor vaccines is demonstrated by the objective evidence submitted by Dr. Spitler. *See* Declaration of Lynn E. Spitler, M.D. Pursuant to 37 C.F.R. § 1.132, submitted April 29, 1998. In this declaration, Dr. Spitler attested to the results of five clinical trials using recombinant human PSA, which has been trademarked Onco Vax P™. First, every aspect of the vaccine as used in the clinical trial is disclosed in the specification as filed. The expression system, a baculovirus system, is described at page 6, line 14 to page 7, line 6 and at page 11, lines 5-11 of the specification. Spitler uses one of the species in the claimed genus of over represented antigens on prostate cancer, namely PSA. PSA is disclosed at page 8, line 18 to page 9, line 11. The vaccine composition, *i.e.,* liposomes, is disclosed at page 14, lines 9-23 and at page 16, lines 13-18. The route of administration, *i.e.,* intramuscular, is disclosed at page 16, lines 1-3. The dose (100 μg) and volume (1 ml) administered is disclosed at page 16, lines 19-23. The sequential administration on a monthly basis is disclosed at page 16, lines 24-27 and at page 17, lines 8-12, respectively. Therefore, in every aspect of the clinical trial, Applicants relied on the guidance and examples provided in the specification as filed. Second, the clinical trials using the PSA vaccine was successful, *i.e.*, administration of the vaccine conferred a therapeutic benefit to the patient. Patients in all of the studies demonstrated PSA-specific T cell responses *in vitro* and *in vivo* with the patients in the fifth clinical study demonstrating dramatic and consistent T cell responses. Dr. Spitler's declaration describes the status of the patients in the 5th clinical trial as all having undergone previous treatment, and three of the five patients having metastatic growth in the bone. Notably, in this patient cohort, all five patients evidenced a clinical response to the vaccine. In four of the five patients, the disease stabilized (*i.e.*, did not continue to grow), while one showed improvement (*i.e.*, improved bone scan in patient 2). This is definitive evidence of the *in vivo* operability of the claimed invention.

Appellants submit that the successful use of PSA to obtain clinical relevant responses in a patient cohort that has undergone previous treatment is sufficient to predict to the skilled artisan that other antigens in the class of over represented prostate antigens would elicit similar responses.

The Examiner cites a variety of reasons why protein vaccine efficacy is unpredictable, including proteolytic degradation, failure to reach target area, and potential adverse effects including cross-reactivity with kallikrein family members. *See* Paper No. 33, pages 6 and 8. However, the PSA in the vaccine used by Spitler is a protein. The successful clinical response to the vaccine indicates that PSA was not prematurely degraded, reached the desired target area, and elicited no potential adverse effects such as cross-reactivity with kallikrein family members. To date, the Examiner has provided no scientific rationale or publications that support the assertion that the results obtained using the PSA antigen vaccine is somehow unique and thus inapplicable to other over represented prostate antigens such as PSMA and PAP. In fact, the Examiner continues to argue that PSA will not work as a tumor vaccine. On page 8 of Paper No. 33, the Examiner looks to canine and Dunning rat models, stating that the secreted form of PSA may reduce immunoglobulin responses and/or anergize T cells, result in cross-reactivity to other kallikrein family members, or induce autoimmunity. This argument appears to indicate that the Examiner doubt the evidence of truth or accuracy of the evidence of record and therefore has given the declaration no weight whatsoever. Appellants submit that the Examiner has failed to provide any basis for questioning the validity of the evidence presented by Dr. Spitler. *In re Marzocchi* 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

Reliance on Hodge et al. (*Int. J. Cancer* 63:231-37 (1995)) does not justify the Examiner's failure to give sufficient weight and consideration to the evidence submitted by Dr. Spitler. In fact, continued reliance on Hodge reflects the fundamental lack of understanding of the scientific principles involved in the instant inventions. Hodge discloses the use of a PSA vaccine to elicit an antitumor response in a primate model by administering PSA as a nucleic acid in a recombinant vaccinia virus. Hodge opines regarding the efficacy of the tumor vaccine consists of whole prostate adenocarcinoma cells admixed with adjuvant, stating that little therapeutic benefit has been achieved with such vaccines. *See* Hodge, page 231, column 1. However, as previously stated, cell-based vaccines are fundamentally distinct in operation from protein-based vaccines. First, the whole cell antigen can act as its own antigen presenting cell. As the Office undoubtedly recognizes, the elicitation of immune response using antigen presenting cells that are MHC-mismatched at one or more loci results in a fundamentally different response that can be less antigen specific, of shorter duration, and thus ultimately less effective. The antigen of the claimed methods,

on the other hand, employs self antigen presenting cells, permitting the maximal elicitation of an antigen-specific response. A skilled artisan does not equate cell-based vaccines with purified antigen-based vaccines as demonstrated by the evidence of record. More specifically, Dr. Spitler attested to the use of Hodge by the Examiner, stating:

> I note that The Examiner makes the point several times that previous attempts to actively immunize patients with prostate adenocarcinoma cells admixed with adjuvant have shown little or no therapeutic benefit. However, the use of whole tumor cells is not analogous to the use of recombinant protein such as purified PSA. Whole PSA is not represented on the surface of the tumor cells; thus, the patients would not be expected to be effectively immunized to PSA via this approach. PSA is synthesized within the tumor cells and secreted; therefore, the patients' immune system might be exposed to small amounts of PSA through this approach as some of the tumor cells die and release the internal PSA; these small amounts of antigen would be presented to the immune system in the context of all the other antigens present on and in the tumor cells. This would not be likely to result in an immune response to the PSA. Peptides derived from PSA are present on the surface of the tumor cells, presented in the context of HLA molecules. For these to induce an immune response, it would be expected that they would have to be taken up by the professional antigen presenting cells and represented on the surface of these cells. Again, this would be occurring in the presence of all the other antigens present on and in the tumor cells.
>
> Thus, one cannot take failure of the approaches using whole tumor cells to indicate that immunization with specific antigens will fail (including antigens overrepresented in the prostate gland, an immunologically effective portion thereof, or an antiidiotypic antibody). Indeed, it is the recognition that the use of pure antigens may represent a more effective means of immunization for cancer therapy which has led to intense activity in this field and numerous clinical trials (Spitler, L.E., Engineered Vaccines for Cancer, *Sixth International Congress on Anti-Cancer Treatment* (1995) Paris, February 6-9, 1996; Spitler, L.E., Cancer Vaccines: The Interferon Analogy, *Cancer Biotherapy* (1995) 10:1-3 ... .

See Declaration of Lynn E. Spitler Pursuant to 37 C.F.R. § 1.132 submitted November 4, 1996, ¶¶ 2-3 (emphasis added). To date, the Examiner has provided no explanation as to why Hodge continues to be relied upon in view of Dr. Spitler's declaration and the state of the art regarding cell versus protein based vaccines.

Likewise, neither Ezzell (*J. NIH Res.* 7:46-49 (1995)) nor Peshwa et al. (The Prostate 1998) supported the Examiner's assertion of unpredictability. Both Ezzell and Peshwa address the limitations of tumor vaccines using cellular compositions, and therefore are inapplicable to the instant invention. The Examiner states that it is "well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes", citing to Ezzell, again demonstrating a lack of fundamental understanding regarding the scientific principles behind the instant invention. The claimed methods do not employ unique tumor antigens, but rather use antigens that are expressed on both normal and malignant prostate tissue. Thus, the optimism of efficacy for immunotherapy using unique tumor antigens is not relevant to the predictability of the present invention. Similarly, Peshwa employs a cellular vaccine where whole dendritic cells are administered after pulsing the live cells with PSMA peptides, and thus the experimentation required to use such a vaccine is irrelevant to the predictability of the instant invention using antigen vaccines.

Finally, Spitler (*Cancer Biother.* 10:1-3 (1995)) clearly supports the credibility and the predictability of the claimed invention when read in its entirety.

In particular, Spitler states that

> [I]nvestigators working in the university setting using vaccines to treat cancer patients have occasionally seen clinical responses to this therapy, which at times has been dramatic. Almost everyone working in this field has had the experience of seeing a dramatic regression of metastatic disease following vaccine therapy. There are numerous published reports of these responses as well as unpublished observations of individual investigators. (emphasis added)

While Spitler opines regarding the future of tumor vaccines, the Office has selected a single sentence that, in fact, mischaracterizes Spitler's point – that active components of vaccines are identified and purified and are now available for routine vaccine protocols. Hence, when read in its entirety, Spitler does not support the Examiner's contention that the successful use of antitumor vaccines would not be credible to a skilled practitioner or that undue experimentation is required to practice the claimed invention.

Hence, Appellants submit that in the references cited to support the allegations of unpredictability are either scientifically irrelevant or misconstrued, and therefore do not credibly support the Examiner's position. Moreover, to date the Examiner has failed to provide cogent,

scientific reasoning to explain the lack of weight given to Dr. Spitler's declaration. For example, the Examiner has not provided any reference which equates cell-based vaccines with purified protein vaccines. Appellants respectfully note that "[t]he examiner should **never** make the determination [of enablement] based on personal opinion. The determination should always be based on the weight of all of the evidence." MPEP § 2164.05 (emphasis included).

D. The evidence of record definitively demonstrates that the person of skill in the art recognizes the disclosure of PSA as enabling for the genus of over represented antigens and immunologically effective portions thereof.

According to the Brief issued by the Board of Patent Appeals and Interferences entered on January 31, 2001, the Examiner "should take a step back and review the merits of the rejections in light of all the evidence now of record [and] issue an appropriate Office action setting forth the facts and reasoning used to support such a rejection." *See* Paper 28, page 4. To date, the Examiner has not substantively addressed the Declarations submitted by Drs. Livingston, Bystryn, Mastrangelo, and Oldham, particularly with regards to the enablement and predictability of the claimed methods for other over represented prostate antigens like PSA.

Appellants submit that the Declarations of Drs. Livingston, Bystryn, Mastrangelo, and Oldham should be given significant weight because each is a person skilled in the art of tumor vaccines. *See* Declaration of Phillip O. Livingston, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996; Declaration of Jean Claude Bystryn, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996, Declaration of Michael Mastrangelo, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996, and Declaration of Robert Oldham Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996. Collectively, these four individuals represented a total of 86 years of scientific experience and expertise in the field of tumors vaccines resulting in a total of over 500 publications in 1996 (the date of submission of the Declarations). In each case, these skilled artisans reviewed the data in Dr. Spitler's Declaration submitted in 1996 as well as the results from the clinical study. *See* ¶2 of each Declaration. Specifically, each of the declarants attest to the following:

> 5. In my opinion, the results obtained in this clinical study provide evidence that the vaccines are likely to be effective in exerting a

> beneficial effect on patients with prostate tumors or at risk for prostate tumors.[1]
>
> 6. The efficacy shown for the vaccine tested in the foregoing clinical studies further provides evidence that analogous vaccines based on host tissue antigen, such as prostate specific membrane antigen (PSMA) and prostate acid phosphatase (PAP) would behave in a similar manner. It is also known that if the entire antigen is effective as a vaccine, portions of the antigen may be effective as well, especially if manipulated by art-known methods to enhance their immunogenicity, such as by coupling them to carrier.

In other words, four skilled artisans with years of experience and extensive publication records recognized that the results with PSA vaccine were predictive for vaccines using other over represented prostate antigens (or host antigens) as well as for immunologically effective portions thereof. While the Examiner cites two publications using immunologically effective portions of over represented prostate antigens to support his assertion of unpredictability, there is no explanation or reasoning given why there is no weight given to these declarations where skilled artisans attest to the predictability of the identifying immunologically effective portions of these antigens. *See* Paper No. 33, page 9, ¶¶ 2-4. Appellants submit that these declarations strongly support the predictability of using any over represented prostate antigen in the vaccine as disclosed in the instant specification because of the necessary common characteristics shared by these antigens, *i.e.*, substantially unique expression in the prostate. To date, the Examiner has provided no reasoning or valid scientific evidence why these Declarations are unpersuasive.

For all of the reasons stated above, the enablement rejection under 35 U.S.C. § 112, first paragraph may be properly withdrawn.

Issue 3: Claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40 particularly point out and distinctly claim the subject matter that Appellants regards as the invention.

Claims 1-14 and 21-40 were rejected as failing to meet the definiteness requirement. *See* Paper No. 33, pages 10-11. According to the Action, the term "over represented" is a relative term

[1] Appellants note that full text of Dr. Livingston's declaration at paragraph 5 is as follows: In my opinion, the results obtained in this clinical study provide evidence that the vaccines are likely to be effective in exerting a beneficial effect

that renders the claim indefinite because the specification does not provide a standard for ascertaining the relative degree and therefore the skilled artisan would not be reasonably apprised of the metes and bounds of the invention. Appellants assert this rejection is in error.

A. Legal standard of the definiteness requirement.

The definiteness requirement of 35 U.S.C. § 112, second paragraph serves to notify the public of the scope of the patentee's right to exclude as well as to provide a clear measure of what the applicant considers the metes and bounds of the invention. MPEP § 2173. The degree of precision required is one that reasonably apprises the skilled artisan of the scope of the invention and is as precise as the subject matter permits. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 95 (Fed. Cir. 1986), *cert. denied* 480 U.S. 947 (1987) ("The claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matters permits. As a matter of law, no court can demand more."). The use of a relative term fails to automatically render a claim indefinite. MPEP § 2173.05(b). Thus, a relative term or words of degree in a claim are not indefinite if the specification provides a standard for measuring that degree that fully informs one of ordinary skill in the art of the metes and bounds of the claimed invention. *Seattle Box Co., Inc. v. Industrial Crating & Packing, Inc.* 221 U.S.P.Q. 568 (Fed. Cir. 1984), *later appeal* 225 U.S.P.Q. 357 (Fed. Cir. 1985).

B. The specification provides a standard for identifying an antigen as "over represented."

The standard for identifying an antigen as over represented is sufficiently precise that one of ordinary skill in the art would understand the scope of the antigens useful in the claimed methods and compositions. Appellants respectfully submit that the standard for identifying such antigens is plainly defined in the specification at page 9, line 21 to page 10, line 2, disclosing:

> The foregoing list of known antigens which are overrepresented on prostate: prostatic acid phosphatase (PAP); prostate specific antigen (PSA); and prostate specific membrane antigen (PSMA) is offered for the purpose of illustration. These well known antigens (or the epitope bearing

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on patients with prostate tumors or at risk for prostate tumor, though much further work will be required to increase the frequency and potency of the responses.

> fragments thereof) are proteins (or peptides) and are useful in the vaccine of the invention. However, the invention includes any other antigens substantially uniquely present on the prostate gland so that prostate derived tissue can be distinguished from other tissue by virtue of the presence of these antigens." (emphasis added)

First, the skilled artisan would readily understand the scope of the term "over represented antigen" in view of the exemplary antigens provided. At the time of filing, the prior art recognized PAP, PSA, and PSMA as antigens that were essentially prostate-specific. For example, in a medical textbook, it states that "[b]oth prostate-specific antigen [PSA] and prostatic acid phosphatase [PAP] are found by immunohistochemical techniques in normal ... and neoplastic prostatic glandular epithelium." Peterson, *The Urinary Tract and Male Reproductive System* IN 17 PATHOLOGY 928 (Rubin and Farber, eds. 1988). A prior art publication states that "the [PSMA] antigen is expressed exclusively by normal and neoplastic prostate cells and metastases." Israeli et al., *Cancer Res.* 53(3):227-30 (1993). In other words, the prior art recognized each of the disclosed illustrative antigens as prostate-specific, and not cancer specific, antigens at the time of filing.

Second, the specification discloses a standard that readily apprises the skilled artisan of the identity of other antigens that are over represented in the prostate. Quite simply, other useful antigens are those substantially uniquely present on normal prostate tissue to a degree that the prostate derived tissue can be distinguished from other non-prostate tissue by virtue of the presence of these antigens. Such relative terminology is commonplace and readily understood by the skilled artisan, and therefore more precise language is not required. One of skill in the art can readily ascertain the expression of an antigen through a variety of well known and routine techniques that include immunohistochemistry and flow cytometric analysis. Thus, the specification directs the skilled artisan to antigens that are prostate-specific by virtue of an almost exclusive expression on normal prostate tissue. As relative levels of antigen expression is easily determined and routinely used to identify tissues, such disclosure fully informs the skilled artisan of the scope of the antigens that are useful in the claimed methods and compositions.

Because the specification reasonably apprises the skilled artisan of the scope of the invention and is as precise as the subject matter permits, the term "over represented" is sufficiently definite when read in light of the specification. For these reasons , the indefiniteness rejection under 35 U.S.C. § 112, second paragraph may be properly withdrawn.

Issue 4: Claims 1-14 and 21-40 are nonobvious.

Claims 1-14 and 21-40 were rejected as obvious under 35 U.S.C. § 103 (a) over the combination of Spitler (U.S. Patent 5,783,867) in view of Israeli *et al.* (U.S. Patent 5,538,866), Horoszewicz (U.S. Patent 5,162,504), Andriole *et al.* (*Ann. Rev. Med.* 42: 9-15 (1991)) and in view of the art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley *et al.* (*Sem. Surg. Oncol.* 5: 293-301 (1989)). Spitler discloses antitumor vaccine compositions and methods useful for the prevention and treatment of a variety of cancers, using tumor antigens that are associated on multiple tumor types. Israeli discloses a form of passive tumor immunotherapy, *i.e.*, therapeutic agents comprising an antibody directed to PSMA that is conjugated to a cytotoxic agent. Horoszewicz relates to passive immunotherapy using prostate-specific antiidiotypic antibodies. Andriole relates to various forms of treatment for prostate cancer other than immunotherapy. McCarley discloses antibodies against prostate antigens that are useful in passive immunotherapy.

The Office has cited a conglomeration of references that do not teach or suggest (1) active immunotherapy using antigens expressed by normal prostate tissue as in the claims of Group I or (2) vaccine compositions comprising over represented antigens as in the claims of Group II. Therefore, Appellants assert that this rejection is in error.

A. Legal standard of the nonobvious requirement.

A *prima facie* case of obviousness requires the satisfaction of three requirements. First, the combined references must teach or suggest all of the claim limitations. Second, the references must provide a suggestion or motivation to modify the teachings or combine the references either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. Third, the reference must provide a reasonable expectation of success. MPEP § 2143.

More specifically, the obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Critical elements of the invention as a whole which clearly

distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Any disclosure teaching away from the claimed invention also must be considered in the obviousness analysis. MPEP § 2142.01. The fact that an invention can be modified is insufficient to establish *prima facie* obviousness in the absence of a suggestion or motivation to make such a modification. *Id.* Furthermore, if a modification changes the principle of operation of a reference, the teachings of that reference do not render the claimed invention obvious. *Id.* Finally, in the analysis of prior art references, it is improper to exercise hindsight to select bits and pieces from the references to create a motivation to modify that is not found in the references, but only in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Simply stated, the suggestion or motivation to modify a reference must be found in the prior art.

Appellants respectfully submit that a *prima facie* case for obviousness has not been presented. The claimed methods relate to the use of antigens over represented on normal prostate tissue, to induce an active antitumor response in a subject. Therefore, a *prima facie* case of obviousness requires that the cited combination of references result in the use of antigens over represented on normal prostate tissue to induce an active antitumor response in a subject. The combination of cited references must provide a motivation to combine the teachings of these references to result in the claimed methods, and most importantly, the references must provide a reasonable expectation of success in combining these teachings. For the reasons discussed below, the cited references fail to fulfill these requirements for *prima facie* obviousness.

B. The cited references cannot properly be combined to result in the claimed inventions.

Appellants respectfully submit that the combination of the cited references cannot properly be combined to result in the claimed inventions because the references do not teach or suggest the use of over represented prostate antigens in a subject to elicit an active antitumor response or the vaccine compositions comprising over represented prostate antigens. The Examiner seems to rely on two assumptions: (1) the use of cancer-specific antigens to elicit an antitumor response is equivalent to the use of over represented prostate antigens expressed on normal prostate tissue to elicit an antitumor response; and (2) the use of such antigens to generate diagnostic

antibodies and passive immunotherapy reagents is commensurate with the use of such antigens to induce an active antitumor immune response. Appellants submit that neither Spitler, the other cited references, what is known in the art, nor any combination thereof support these assumptions.

1. **Cancer-specific antigens are not equivalent to the use of prostate-specific antigens expressed on normal tissue.**

Appellants respectfully submit that the prior art references nor the knowledge in the art equate cancer-specific antigens with prostate-specific antigens. Spitler fails to teach or suggest the use of over represented prostate antigens to elicit an antitumor response in a subject, a point as yet unappreciated by the Examiner. In its reliance on Spitler, the Office seems to be asserting that antigens associated with the malignant or transformed cell phenotype *per se* are equivalent to over represented prostate antigens that are substantially uniquely on normal prostate tissue as well as on malignant prostate tissue. The claimed methods use antigens that are substantially organ-specific antigens, expressed on both normal and malignant prostate tissue, and thus are not associated with the malignant nature of the prostate cells or other tumor cells *per se*. Spitler, on the other hand, teaches the use of antigens that are associated with the malignant or metastatic nature of the cells. Specifically, Spitler discloses the use of antigens (*i.e.*, CO-029 and GA733-2) that are each characterized by expression on multiple types of malignant cells. *See* Spitler, at column 2, lines 22-26. Thus, the claimed methods are distinct from Spitler in the choice of antigen. Moreover, the antigens selected are characterized as being expressed on a variety of tumors, not any particular tumor or tissue. In other words, Spitler suggests the use of a pan-epitope to stimulate a general antitumor immune response against any malignant cell. Appellants note that some of the antigens cited by Spitler as exemplary antigens can be found at extremely low levels in normal tissue. However, such expression of these antigens in normal tissue does not permit the antigen to be used as a marker that distinguishes that tissue from any other normal tissue. In other words, these antigens are not ones that are substantially uniquely present on a normal tissue to a degree that that tissue can be distinguished from other normal tissue by virtue of the presence of these antigens as in the instant claims. Thus, contrary to the assertions of the Office, Spitler does not teach the use of the over represented prostate antigens in vaccine compositions of Group II or the methods of Group I.

2. Because active immunotherapy is separate and distinct from passive immunotherapy, there is no motivation to combine Spitler with Israeli, Horoszewicz, and McCarley.

Presumably because Spitler fails to teach the use of the over represented antigens in the instant claims, the Examiner seeks to combine its teachings with those of Israeli, Horoszewicz, and McCarley. However, there is no suggestion or motivation to combine the cited references because passive and active immunotherapy are recognized in the art as functionally and mechanistically distinct. It is well known that passive and active immunotherapy are distinct and separate biological processes, and therefore the skilled artisan would not consider teachings regarding passive immunotherapy applicable to active immunotherapy. For example, this distinction is recognized in the classic text CANCER: PRINCIPLES & PRACTICE OF ONCOLOGY (De Vita et al., eds. 1993). It states that "[s]trategies for the immunotherapy of cancer can be divided into active and passive approaches." *Id.* at page 305. Active immunotherapy is described as "immunization of the tumor-bearing host with materials designed to elicit an immune reaction capable of eliminating or retarding growth." *Id.* Typically, this involves the development of cellular response to the tumor. Passive immunotherapy, on the other hand, is the administration of exogenous antibodies.[2] *Id.* at Table 17-12. Thus, two critical and undeniable distinctions arise. First, active immunotherapy requires the participation of the host immune response, while passive immunotherapy does not. Thus, antigens that may serve as effective targets for passive immunotherapy may in fact be completely non-immunogenic if the same antigen is administered to the host. Such *in vivo* factors as available antigen presenting cells, suppressive cytokines, lack of appropriate co-stimulatory molecules, and identity as self-antigens can contribute to the lack of immunogenicity of such an antigen to its host's immune system.

Second, it is well recognized that humoral and cellular components of the immune system are not superimposable on each other.

> There is a significant difference in the nature of antigens recognized by humoral and cellular detection systems. Humoral antibodies detect specific epitopes on antigenic molecules, and it is the interaction of these molecules with the variable

[2] Passive immunotherapy can also include the exogenous administration of other immune effectors, such as activated lymphocytes. However, such passive immunotherapy still does not require the active participation of the host immune response.

> region of the antibody that produces recognition. In contrast, antigens recognized by T-cell receptors recognize processed peptides on the surface of the tumor cell or on an antigen presenting cell in conjunction with MHC molecules.

Id. at page 301. Effective active immunotherapy protocols typically elicit a cellular response to the immunizing antigen. Thus, the ability to generate antibodies to PSMA or the suggestion to use such antibodies in passive immunotherapy has no relevance to the instant claims drawn to methods and compositions of active immunotherapy of prostate cancer. These recognized distinctions between active and passive immunotherapy and between antibody and T-cell receptor recognition are still cornerstones of tumor immunotherapy today. Moreover, many of the antibodies disclosed in the cited references are of non-human origin. Therefore, they contain no teaching whatsoever regarding the immunogenicity of the same antigen in humans, a critical element of any active immunotherapy strategy. A person of ordinary skill in the art would not be motivated to combine these references because of these well known distinctions. Therefore, the teachings relating to antibodies in Horoszewicz, McCarley, or Israeli do not provide any motivation to combine these references with Spitler.

For example, Israeli and Horoszewicz disclose prostate antigens, but neither reference teaches nor suggests the use of an antigen to elicit an active antitumor immune response or compositions with such a function. Israeli teaches the use of PSMA in passive immunotherapy of tumors. *See* Israeli, at column 12, line 53 to column 13, line 9. Active immunotherapy is not mentioned. Similarly, Horoszewicz teaches the use of prostate antigen-specific antibodies for passive immunotherapy. Horoszewicz's only disclosure of an active immunotherapy protocol does not employ antigen, but uses anti-idiotype antibodies, a fundamentally different therapy (*i.e.*, antigen administration is never required). *See* Horoszewicz, at column 12, lines 21-29. Because Israeli and Horoszewicz do not teach the use of the prostate antigens in active immunotherapy, neither reference alone or in combination with Spitler teach the instant claimed inventions.

Appellants note that the disclosure of anti-idiotype antibody immunotherapy strategy in Horoszewicz cannot cure the deficiency in Spitler. The use of anti-idiotype antibodies in Horoszewicz provides no teaching or suggestion regarding the use of antigens overexpressed in normal host tissues in active immunotherapy. Anti-idiotype antibodies are distinct from antigen-based therapies in at least three aspects: (1) anti-idiotype antibodies elicit an antitumor response to

a single epitope of the antigen, *i.e.*, the binding cleft of the antibody, whereas antigen administration results in response to multiple epitopes; (2) anti-idiotype antibodies do not require processing and presentation by antigen presenting cells, whereas antigen administration is completely dependent on appropriate processing and presentation by antigen presenting cells; and (3) anti-idiotype antibodies are typically foreign to the host, while the instant prostate antigen is self antigen overexpressed on normal host tissue. The person of ordinary skill in immunology recognizes each of these as significant, distinct, and non-overlapping when considering immunotherapy.

Similarly, McCarley has no teaching or suggestion regarding the use of over represented prostate antigens in active immunotherapy. McCarley's teachings are limited the disclosure of a number of monoclonal antibodies that bind various prostate antigens and may be useful for passive immunotherapy (*e.g.*, when conjugated to a chemotherapeutic agent). Therefore, as with the references above, if these references are to be relevant to the claimed inventions, it must be assumed that the ability to elicit antigen-specific antibodies in non-tumor bearing animals using the disclosed compositions is equivalent to eliciting an effective antitumor response in a subject. Such an assumption cannot be supported scientifically. It is well known in the art the immunogenicity required to elicit specific antibodies that simply bind an antigen does not correlate with, and is often distinct from, the ability to elicit an effective antitumor response, whether humoral or cellular. Moreover, the courts have acknowledge that the ability to induce a response to an antigen, such as an antibody response, is distinct from the ability of an antigen to induce an active or immunoprotective response in a host. *See In re Wright* 27 U.S.P.Q.2d. 1510, 1513 (reasoning that a mere antigenic response is distinct from the induction of active immunity that confer protection against the eliciting agent). Thus, these references do not cure the deficiencies in the Spitler reference.

Finally, Appellants note that Andriole actually teaches away from the need for immunotherapy, as acknowledged by the Examiner in his answer. *See* Paper No. 51, page 7 (stating that Andriole teaches that "surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer.").

Appellants respectfully submit that, in point of fact, Spitler teaches away from the claimed methods and compositions. Spitler teaches the need for a vaccine that is "efficacious in the

prevention and treatment of all cancers." Spitler, at column 1, lines 50-51 (emphasis added). Spitler also teaches that the disclosed compositions are those useful "for the prevention and treatment of a variety of cancers." Spitler, at column 2, lines 19-21 (emphasis added). In other words, Spitler discloses the use of antigens associated with the malignant phenotype *per se*, and not normal tissue, in tumor vaccines. The most preferred antigen being one that is expressed on numerous different types of malignant cells. In order for such a vaccine to be effective and non-toxic, the target antigen would not be one expressed on normal tissue. A skilled artisan would recognize that the administration of a prophylactic vaccine that elicits an immune response to an antigen on normal tissues would result in autoimmunity specific for that tissue, a potentially fatal side effect. Alternatively stated, Spitler's teachings require the use of antigens that are not expressed on normal tissues to achieve its intended purpose. Hence, nothing in Spitler teaches the extension of its teachings to antigens expressed in an organ-specific manner in normal tissues alone or in any combination with the references cited by the Office.

Because the modification of Spitler's teachings to include over represented prostate antigens expressed on normal tissues would render the vaccine unsatisfactory for its intended purpose (*i.e.*, prophylactic and therapeutic vaccine), there is no motivation or suggestion to make such a modification. MPEP § 2143.01 at page 2100-124, second column ("if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification") (citations omitted).

In sum, nothing in Spitler, the other cited references, or the art provide a suggestion or motivation to select over represented prostate antigens, as antigens for active immunotherapy. The other cited references that merely disclose prostate antigens in unrelated contexts do not provide any suggestion or motivation to use these antigens in Spitler's methods.

Finally, the references do not provide a reasonable expectation of success in any combination. The majority of the references do not even address active immunotherapy, thus making it impossible for them to convey any expectation of success regarding the methods or compositions of the instant application.

For the reasons stated above, the rejection under 35 U.S.C. § 103(a) may be properly withdrawn.

Issue 5: Whether the claims are unpatentable under the judicially-created doctrine of obviousness-type double patenting over claims 1-8 of U.S. Patent No. 5,925,362 and over claims 13, 15, 16, and 18-24 of co-pending Application Serial No. 09/300,978.

Claims 1-14 and 21-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent 5,925,362. Claims 1-14 and 21-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 15, 16, and 18-24 of copending application Serial No. 09/300,978.

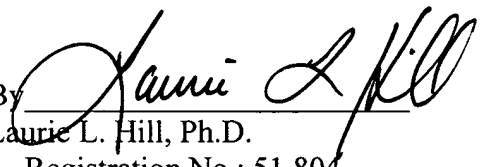
Signed Terminal Disclaimers are submitted herewith as Exhibit A. Therefore, Applicants respectfully submit that the basis for the rejection may be removed.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Dated: February 12, 2004

Respectfully submitted,



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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 08/105,444

1 (Previously presented): A method to induce an antitumor immune response in a potential or actual prostate tumor-bearing subject which method comprises administering to said subject a composition comprising an ingredient which is active to induce said immune response and is selected from the group consisting of

at least one antigen over represented in the prostate gland or an immunologically effective portion thereof; and

an expression system capable of generating *in situ* said antigen.

2 (Previously presented): The method of claim 1 where in said antigen is a protein or peptide.

3 (Previously presented): The method of claim 2 wherein said protein or peptide is selected from the group consisting of prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), prostatic acid phosphatase (PAP) and an immunologically effective portion thereof.

4 (Original): The method of claim 1 wherein said subject is afflicted with metastatic prostate cancer.

5 (Original): The method of claim 1 wherein said subject has been surgically treated to excise said tumor but is at risk for recurrence.

6 (Previously presented): The method of claim 1 wherein said composition is administered to said subject prior to surgical excision of said prostate tumor.

7 (Original): The method of claim 1 wherein said subject is a potential prostate tumor-bearing subject at risk for said tumor.

8 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors in a subject which comprises an ingredient which is active to elicit said immune response, is formulated for parenteral administration and is

an expression system capable of generating *in situ* an antigen over represented on the prostate gland with respect to other tissues or an immunologically effective portion thereof.

9 (Previously presented): The vaccine of claim 8 wherein said antigen is selected from the group consisting of prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), prostatic acid phosphatase (PAP) and an immunologically effective portion thereof.

10 (Original): The vaccine of claim 8 wherein the antigen is encapsulated in a liposome or coupled to a liposome.

11 (Original): The vaccine of claim 10 wherein said liposomes contain an adjuvant or are precipitated with alum.

12 (Original): The vaccine of claim 8 which further includes at least one adjuvant capable of enhancing said antitumor immune response.

13 (Original): The vaccine of claim 12 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria; polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).

14 (Previously presented): The vaccine of claim 8 wherein said expression system consists essentially of DNA encoding said antigen or said portion or wherein said expression system comprises a living expression vector.

15-20 (Canceled)

21 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors in a subject which comprises at least one antigen which is active to elicit said immune response, is formulated for parenteral administration and comprises

said at least one antigen being over represented on the prostate gland with respect to other tissues or an immunologically effective portion thereof,

wherein said antigen is encapsulated in or coupled to a liposome.

22 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors in a subject which comprises at least two ingredients which are active to elicit said immune response and are formulated for parenteral administration, wherein each ingredient is selected from the group consisting of

an antigen over represented on the prostate gland with respect to other tissues or an immunologically effective portion thereof; and

an expression system capable of generating *in situ* said antigen or said portion.

23 (Previously presented): The vaccine of claim 22 wherein said antigen is selected from the group consisting of PSA, PSMA, PAP and an immunologically effective portion thereof.

24 (Original): The vaccine of claim 22 wherein the antigen is encapsulated in a liposome or coupled to a liposome.

25 (Original): The vaccine of claim 24 wherein said liposomes contain an adjuvant or are precipitated with alum.

26 (Original): The vaccine of claim 22 which further includes at least one adjuvant capable of enhancing said antitumor immune response.

27 (Original): The vaccine of claim 26 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria; polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).

28 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors which comprises an ingredient which is active to elicit said immune response, is formulated for parenteral administration, and comprises at least one immunologically effective portion of an antigen over represented on the prostate gland with respect to other tissues said portion being less than the complete antigen.

29 (Previously presented): The vaccine of claim 28 wherein said antigen is selected from the group consisting of prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), prostatic acid phosphatase (PAP).

30 (Previously presented): The vaccine of claim 28 wherein said portion is encapsulated in a liposome or coupled to a liposome.

31 (Original): The vaccine of claim 30 wherein said liposomes contain an adjuvant or are precipitated with alum.

32 (Original): The vaccine of claim 28 which further includes at least one adjuvant capable of enhancing said antitumor immune response.

33 (Original): The vaccine of claim 32 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria; polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).

34 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors in a subject which comprises an ingredient which is active to elicit said immune response, is formulated for parenteral administration, and comprises at least one antigen over represented on the prostate gland with respect to other tissues with the proviso that said antigen is other than human prostate specific antigen (PSA) in a form which is produced in human cells.

35 (Original): The vaccine of claim 34 wherein said antigen is PSA recombinantly produced in nonhuman cells and exhibits posttranslational modifications different from those of PSA produced in human cells.

36 (Previously presented): The vaccine of claim 34 wherein said antigen is selected from the group consisting of PSA, PSMA, PAP and an immunologically effective portion thereof.

37 (Original): The vaccine of claim 34 wherein the antigen is encapsulated in a liposome or coupled to a liposome.

38 (Original): The vaccine of claim 37 wherein said liposomes contain an adjuvant or are precipitated with alum.

39 (Original): The vaccine of claim 34 which further includes at least one adjuvant capable of enhancing said antitumor immune response.

40 (Original): The vaccine of claim 39 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria; polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).

Docket No.: 204372000300
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Lynn E. SPITLER et al.

Application No.: 08/105,444

Filed: August 11, 1993 Art Unit: 1644

For: PROSTATIC CANCER VACCINE Examiner: P. Gambel

APPELLANT'S BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants hereby appeal from the final rejection of claims 1-14 and 21-40 mailed June 11, 2003. A Notice of Appeal was filed along with a Petition for an Extension of Time on November 10, 2003 and was received in the Office on November 12, 2003. The Brief was due on January 12, 2004. A petition for an extension of time of one month until February 12, 2004 is attached hereto, along with the required fee. Appellants respectfully request that the rejection be reversed. In accordance with 37 C.F.R. § 1.192, this Brief is filed in triplicate and is accompanied by the required fee.

Enclosed herewith is the following Exhibit:

Exhibit A: Terminal Disclaimers

I. REAL PARTY IN INTEREST

The present application is assigned to Jenner Technologies, a California Corporation, which was purchased by Immuno-Designed Molecules, a French Corporation.

II. RELATED APPEALS AND INTERFERENCES

There is a pending appeal in the related case, Application Serial No. 09/300,978, which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 34 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 15-20

2. Claims withdrawn from consideration but not canceled: None

3. Claims pending: 1-14, 21-40

4. Claims allowed: None

5. Claims rejected: 1-14, 21-40

C. Claims On Appeal

The claims on appeal are claims 1-14 and 21-40.

IV. STATUS OF AMENDMENTS

Applicant filed an Amendment After Final Rejection on August 11, 2003. The Examiner responded to the Amendment After Final Rejection in an Advisory Action mailed October 3, 2003.

The Amendment After Final Rejection did not contain amendments to the claims. Accordingly, the claims enclosed herein as Appendix A are as of the response filed by the Applicant on March 3, 2003.

V. SUMMARY OF INVENTION

Prior art formulations for vaccines elicit an antitumor response from the host immune system using antigens that are uniquely or largely associated with the malignant or metastatic nature of the tumor cell *per se*. The present invention represents a different approach in that, rather than using antigens associated with a metastatic or malignant phenotype, the present invention employs antigens that over represented or substantially uniquely expressed on normal tissue, namely prostate tissue. *See* Specification, at page 9, line 29 to page 10, line 2. In other words, these antigens are not uniquely associated with the malignant or metastatic nature of the tumor cell, but rather are found on both normal and malignant prostate tissue. *See* Specification, at page 4, lines 11-22. Thus, the invention takes advantage of the fact of the non-essential nature of the prostate organ, and elicits an antitumor immune response that simultaneously eliminates normal and malignant prostate tissue. *See* Specification, at page 4, lines 11-22.

While the prior art recognizes that prostate specific antigen (PSA) can be used in healthy experimental animals to generate antibodies for use in diagnosis, there is no suggestion that PSA or any other antigen over represented on normal prostate tissue can be used to elicit a protective or therapeutic immune response against prostate cancer. According to the prior art, the use of antigens highly expressed on normal and malignant tissues is undesirable because (1) the elicitation of an immune response directed to such an antigen results in the destruction of normal and malignant tissue, a potentially fatal consequence for the successful elimination of a tumor, and (2) elicitation of an immune response to an antigen highly expressed on normal tissue, or a self-antigen, is difficult due to the host immune system's anergy or tolerance to such self-antigens.

Prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), and prostatic acid phosphatase (PAP) are three representative species of the genus of over represented antigens specifically expressed in normal prostate tissue that are useful in the present invention. *See* Specification, at page 7, line 12 to page 10, line 2. The antigens of the present invention can be supplied, for example, as the antigen *per se* or as an expression system which is able to produce the protein or immunologically effective peptide *in situ* in the subject. *See* Specification, at page 10, line 3 to page 12, line 19. The invention is directed to methods of use and pharmaceutical vaccine compositions. *See* Specification, at page 13, line 16 to page 15, line 17.

Thus, the invention of claims 1-3 is directed to methods of eliciting an effective antitumor immune response to prostate tumors in a subject bearing or potentially bearing a prostate tumor using antigens that are overexpressed on normal prostate tissue, such as PSA, PSMA, and PAP. Claims 5-8 further defines the method as being directed to a subject afflicted with prostate cancer and/or wherein the tumor of the subjects has been surgically excised, but is still at risk for recurrence. The invention of claims 9-14 and 21-40 is directed to pharmaceutical or veterinary compositions for eliciting an effective antitumor immune response to prostate tumors in a subject bearing or potentially bearing a prostate tumor using antigens that are overexpressed on normal prostate tissue. One or more of the prostate antigens can be delivered as a protein or immunologically effective portion thereof or an expression system that produces such a protein or immunologically effective portion thereof. Claims 10-13, 24-27, 30-33, and 37-40 are directed to the same composition where either the antigen is further encapsulated in a liposome or coupled to a liposome and/or the liposome contains an adjuvant.

VI. ISSUES

The following issues are presented for review:

1. Whether the instant specification sufficiently describes the "antigen over represented in the prostate gland or an immunologically effective portion thereof," "nucleic acid that generates said antigen or antigens in situ", "proteins", or "peptides" of the claimed methods and compositions in a manner that reasonably conveys possession of the subject matter to the skilled artisan, as reflected in the rejection of claims 1-14 and 21-40 under 35 U.S.C. § 112, first paragraph.

2. Whether the instant specification reasonably enables any "over represented prostate specific antigen", any "immunologically effective portion thereof", "protein", or "peptide" as reflected in the rejection of claims 1-14 and 21-40 under 35 U.S.C. § 112, first paragraph.

3. Whether the claims particularly point out and distinctly claim the subject matter that Appellant regards as the invention as reflected in the rejection of claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40 under 35 U.S.C. § 112, second paragraph.

4. Whether the claims are obvious under 35 U.S.C. § 103 (a) over the combination of Spitler (U.S. Patent 5,783,867) in view of Israeli *et al.* (U.S. Patent 5,538,866), Horoszewicz (U.S. Patent 5,162,504), Andriole *et al.* (*Ann. Rev. Med.* 42: 9-15 (1991)) and in view of the art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley *et al.* (*Sem. Surg. Oncol.* 5: 293-301 (1989)).

5. Whether the claims are unpatentable under the judicially-created doctrine of obviousness-type double patenting over claims 1-8 of U.S. Patent No. 5,925,362 and over claims 13, 15, 16, and 18-24 of co-pending Application Serial No. 09/300,978.

VII. GROUPING OF CLAIMS

The inventive concept of the claims lies in the following groups: Group 1 (claims 1-7) drawn to methods of inducing an antitumor response using over represented prostate antigens, and

Group II (claims 8-14 and 21-40) drawn to vaccine compositions comprising over represented prostate antigens. While Applicants maintain that the claimed inventions of both groups of claims are patentable, the case law seems to suggest differing standards in assessing the patentability of method and composition claims. Thus, for the purposes of the rejections under 35 U.S.C. §§ 112, first paragraph and 103 (a), as set forth in Issues 1, 2, and 4, the claims in Group I and II should be considered separately. It should be evident that the rejection under 35 U.S.C. § 112, second paragraph, as set forth in Issue 3 above, is applicable to claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40. Issue 3 relates to whether the claims particularly point out and distinctly claim over represented antigens. All claims may be considered together for the purposes of the rejection under the judicially created doctrine of obviousness-type double patenting as set forth in Issue 5.

VIII. ARGUMENTS

It is believed that all issues should be resolved in favor of Appellants for the following reasons:

Issue 1: Claims 1-14 and 21-40 are sufficiently described in the instant specification to reasonably convey to the skilled artisan possession of the over represented antigens in the prostate gland or an immunologically effective portion thereof, nucleic acids that generate these antigens as well as proteins and peptides of over represented antigens at the time of filing.

Claims 1-14 and 21-40 were rejected as lacking sufficient written description in the specification to reasonably convey to a person of skill in the art possession of the claimed methods and compositions at the time of filing. *See* Paper No. 33, pages 2-5. According to the Action, the disclosure of whole PSA, PSMA, and PAP and the accompanying disclosure of relevant, identifying characteristics of the genus is insufficient to fully describe the genus of over represented prostate antigens, immunologically effective portions thereof, nucleic acids that generate these antigens, and the associated proteins and peptides useful in the claimed methods and compositions. Appellants assert this rejection is in error.

A. Legal standard of the written description requirement

The written description requirement prevents an applicant from later asserting that he invented which he did not. *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cir. 1991). In other words, the "description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented [or had possession of] what is claimed." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). Possession of the invention can be shown by actual reduction to practice or showing that the invention was ready for patenting through the description of sufficiently distinguishing characteristics. *See Pfaff v. Wells Electronics, Inc.*, 48 U.S.P.Q.2d 1641, 1647 (1998) (emphasis added). The adequacy of the description is measured by the understanding of one of ordinary skill in the art. *Id.* Therefore, the fulfillment of the written description requirement is a fact-based inquiry that necessarily varies depending on the nature of the invention. *Enzo Biochem v. Gen-Probe, Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002).

The written description requirement for a genus requires only a sufficient description of a genus of a representative number of species by actual reduction to practice, reduction to drawing, or by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus to one of skill in the art. *Manual of Patent Examination Procedure* (hereinafter "MPEP") § 2163(II)(A)(3)(a)(ii) (8th Ed. 2001). A representative number of species is that number that adequately represents the genus and is an inverse function of the skill and knowledge in the art. *Id.* Thus, the description must be such that the person of skill in the art recognizes that the inventor was in possession of the necessary common attributes or features of the elements possessed by members of the genus, providing a measure of predictability for the utility described for the genus. *Id.* (emphasis added).

B. The specification sufficiently discloses of the genus of over represented antigens and immunologically effective portions thereof to the person of skill in the art.

The disclosure clearly allows one of skill in the art to recognize that Appellants had possession of the invention at the time of filing through (1) the disclosure of the necessary common attribute or feature of the antigens used in the claimed methods of Group I and compositions of Group II, and (2) the disclosure of three representative genus members, namely PSA, PSMA, and PAP, and thus fulfills the written description requirement under 35 U.S.C. § 112, first paragraph.

Appellants respectfully submit that the specification as filed sufficiently discloses the necessary common attribute or feature of the antigens uses in the claimed methods and compositions. *See Pfaff v. Wells Electronics, Inc.*, 48 U.S.P.Q.2d 1641, 1647 (1998) (holding that possession of the invention can be shown by actual reduction to practice or showing that the invention was ready for patenting through the description of sufficiently distinguishing characteristics). First and foremost, Appellants explicitly identify the necessary common attribute of these antigens - they are over represented on normal prostate tissue while also being expressed on malignant prostate tissue. More specifically, the specification discloses that the antigen useful in the claimed invention is one that is over represented or substantially uniquely present on prostate gland so that prostate derived tissue can be distinguished from other tissue by virtue of the presence of these antigens. *See* specification at page 9, line 29 - page 10, line 2. The specification further discloses that the concentration or representation of this antigen is sufficiently higher in normal prostate tissue relative to other normal tissues so that "the prostate can be effectively targeted by the immune response raised against this antigen with relative sparring of other organs or tissues." *See* specification at page 5, lines 15-24. One of skill in the art would readily recognize that such an antigen is expressed almost exclusively, *i.e.*, substantially uniquely, on normal prostate tissue at such a level that an immune response elicited against that antigen results in the simultaneous elimination of normal and malignant prostate tissue. Second, the specification further describes the genus of useful antigens through the disclosure of three representative antigens: PSA, PSMA, and PAP. Each of these antigens is a protein and is substantially uniquely expressed or over represented on normal prostate tissue such that the antigen expression profile distinguished the prostate tissue from other tissues. *See* specification at page 7, line 13 to page 9, line 21. Moreover, this expression

profile is recognized in the prior art. *See, e.g.*, Peterson, *The Urinary Tract and Male Reproductive System* IN 17 PATHOLOGY 928 (Rubin and Farber, eds. 1988) (stating that "[b]oth prostate-specific antigen [PSA] and prostatic acid phosphatase [PAP] are found by immunohistochemical techniques in normal ... and neoplastic prostatic glandular epithelium"); Israeli et al., *Cancer Res.* 53(3):227-30 (1993) (stating that "the [PSMA] antigen is expressed exclusively by normal and neoplastic prostate cells and metastases"). Therefore, the disclosure in the specification clearly identifies the antigens for use in the present claims to the person of skill in the art.

Moreover, Appellants submit that the standard applied to the claims of Group I by the Examiner appears to be one that would be applicable to claims drawn to novel over represented antigens *per se*. However, such is not the appropriate standard for the instant claims. In fact, the courts have repeatedly held that for claims drawn to the use of known compounds in a manner auxiliary to the invention, the written description must only be so specific as to lead the skilled artisan to that class of compounds.

The Federal Circuit's predecessor court, the Court of Customs and Patent Appeals, repeatedly recognized a standard for claims drawn to known compounds used in a manner auxiliary to the claimed methods distinct from that applied to claims drawn to novel compositions *per se*, a standard that has not been disturbed by the Federal Circuit. For example, in *In re Fuetterer*, the court examined claims drawn to a rubber stock composition useful in producing tire treads with a limitation of including "an organic salt" capable of maintaining an homogeneous distribution of another component in the composition. 138 U.S.P.Q. 217 (C.C.P.A. 1963). The specification disclosed the function desired and four members of the genus having the recited function. The court held that the disclosure fulfilled the written description requirement because there is "nothing in patent law which requires appellant to discover which of all those salts have such a property and which will function properly in the combination." *Id.* at 223. The court then specifically recognized that such claims did not exclude additional organic salts discovered in the future with the cited properties, saying

> If others in the future discover what organic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some organic salt not named by appellant in his disclosure.

Id. (emphasis added).

Likewise, in *In re Herschler*, the court held that claims drawn to the use of a mixture of DMSO with a physiologically active steroidal agent in a therapeutic method was sufficiently described by a generic definition and a single disclosed example. 200 U.S.P.Q. 211 (C.C.P.A. 1979). In the application at issue in *Herschler*, the court sought to determine whether an earlier filed application qualified as a proper priority document for claims to physiologically active steroidal agents. In the earliest filed application, steroidal agents were not disclosed *in haec verba.* This application provided a single example using a corticosteroid with DMSO and a definition of the term "physiologically active substance." *Id.* at 716-717 (defining the term as "any substance which has a demonstrable and desired physiological activity in the sense that animal tissue responds thereto"). The court held that

> claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one of ordinary skill in the art to that class of compounds.

Id. at 718 (emphasis added). The court reasoned that the functional description of the compounds useful in the claimed methods and compositions was sufficient description since the claims were not drawn to novel steroidal agents. *Id.* at 717. As in *In re Fuetterer*, the court recognized that the compounds useful in the DMSO method was much broader than the diversity of compound disclosed in the application, but nonetheless held that "one having ordinary skill in the art would have found the use of the subgenus of steroids to be apparent from the written description [provided]." *Id.* Thus, the class of compounds useful in the claimed methods and compositions necessarily included any future identified compounds with the identified characteristic, *i.e.*, being physiologically active.

The claims of the instant application are analogous to those of *In re Fuetterer* and *In re Herschler*. The patentability of the instant invention lies not in the identification of novel prostate antigens, immunologically effective portions thereof, or prostate proteins or peptides, rather in knowing what to do with the prostate antigens that have the disclosed physical and functional characteristics. Alternatively stated, the specific identity of the prostate antigens used is auxiliary to the invention of the claimed methods and compositions beyond the necessary common attribute disclosed. Because the specification clearly leads the skilled artisan to this class of antigens through

the specific, necessary physical and functional characteristics and the disclosed examples, the instant written description is sufficient. Likewise, the compositions of Group II are sufficiently identified by their common necessary attribute.

Because the specification clearly leads the skilled artisan to this class of antigens through the specific, necessary physical and functional characteristics and the disclosed examples, the instant specification is sufficient for the claims of Groups I and II.

C. Neither *Fiers*, *Fiddes*, nor *Eli Lilly* are applicable to the instant invention.

Fiers, *Fiddes*, and *Eli Lilly* are distinct from the instant invention because the claimed invention in each of theses cases is a novel DNA sequence. While conception and reduction to practice of a novel DNA sequence may require the identification of the actual DNA sequence being claimed, it does not follow that the requirement for the recitation of DNA sequence is applicable to claims involving a method using proteins and DNA sequences where the patentability of the method lies in the method itself, not in a particular protein or DNA sequence. All functional descriptions of genetic material do not fail as a matter of law. *Amgen, Inc. v. Hoeschst Marion Roussel, Inc.*, 65 U.S.P.Q.2d 1385, 1398 (Fed. Cir. 2003). Rather the court looks to the knowledge in the art and whether the terms are such that an ordinary skilled artisan would comprehend the invention. For reasons articulated *infra*, Appellants submit that the skilled artisan would recognize the Appellants had possession of what is claimed, particularly for the invention of the claims in Groups I. Therefore, the requirement for a specific DNA sequence by the courts in *Fiers*, *Fiddes*, and *Eli Lilly* does not apply to the instant methods.

For the reasons stated above, the written description rejection under 35 U.S.C. § 112, first paragraph may be properly withdrawn.

Issue 2: The specification provides sufficient guidance for one of skill in the art to make and use the methods and compositions of claims 1-14 and 21-40.

Claims 1-14 and 21-40 were rejected as failing to meet the enablement requirement. *See* Paper No. 33, pages 5-10. According to the Action, Applicants have not provided sufficient enabling disclosure regarding (1) any over represented prostate specific antigen, (2)

immunologically effective portions of over represented prostate specific antigens, or (3) protein or peptides of these antigens. Appellants assert this rejection is in error.

A. **Legal standard of the enablement requirement.**

Enablement under 35 U.S.C. § 112, first paragraph requires that the specification of a patent teach one of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright,* 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993). Undue experimentation is determined by a series of factual inquiries that can include the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). While working examples are one consideration in the analysis, compliance with the enablement requirement does not turn on whether a working example is disclosed. MPEP § 2164.02. In fact, a lack of evidence that the invention works as claimed, standing alone, is an insufficient reason to reject a claimed invention on lack of enablement. *Id.*

Thus, the specification must be enabling to one of skill in the art. MPEP § 2164.05(b). Thus, the amount of guidance or direction required to fulfill the enablement requirement is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 91, 94 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 947 (1987) (holding that a specification need not disclose what is well known in the art).

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art ... would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could use the genus as a whole without undue experimentation.

MPEP §2164.02.

B. The specification supports the breadth of the claimed invention.

The specification reasonably enables the use of the genus of over represented antigens, immunologically effective portions thereof, encoding nucleic acids, and proteins and peptides in the claimed methods and compositions. The specification provides adequate guidance as to the identity of the antigens useful in the claimed methods and compositions. The specification provides three representative examples in the genus of over represented antigens, *i.e.*, PSA, PSMA, and PAP as well as an explicit, specific definition for the genus. Antigens in this genus are those that are substantially uniquely present on the prostate gland so that prostate derived tissue can be distinguished from other tissue by virtue of the presence of these antigens and that can serve as a target for an immune response with relative sparring of other organs or tissues. *See* Specification at page 9, line 29 - page 10, line 2 and page 5, lines 15-24. Moreover, each of the antigens disclosed is a protein. One of skill in the art would recognize these antigens as host antigens, *i.e.*, expressed on normal tissue, whose expression level is a distinguishing feature of prostate tissue and therefore allows a targeted immune response to eliminate the prostate tissue (normal and malignant) with relative sparring of other tissues.

Appellants respectfully submit that further biochemical information on members of the genus of over represented antigens useful in the claimed methods and compositions is not required for the reasonable enablement of the methods and compositions because the antigens are not defined by biochemical properties, but rather by level of expression on normal prostate tissue. Identifying biochemical information is not required. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63, U.S.P.Q.2d 1609, 1613 (2002). It is only necessary that the antigens be described in a way that permits the person of skill in the art to identify the class of antigens useful in the methods and compositions. The antigens are sufficiently identified as antigens substantially uniquely expressed on prostate tissue to inform the skilled artisan of their identity. To date, the Examiner has provided no scientific explanation or scientific publication to support his allegation that the physical/functional characteristics provided by the specification are insufficient for the skilled artisan making and using the claimed invention.

Second, the specification teaches the skilled artisan how to make, formulate, and administer full-length antigens, immunologically reactive portions thereof, and nucleic acids

encoding one or more of those antigens *in situ*. On page 10, line 9 to page 12, line 2, the specification teaches the skilled artisan how to prepare antigens. On page 12, lines 3-23, the specification teaches the skilled artisan how to generate immunologically effective portions of the antigens. Examples of generating the antigens *in situ* by an expression system are set forth on page 6, line 21 to page 7, line 14. On page 16, line 24 to page 17, line 4, the specification provides an example of a viral expression vector for the claimed nucleic acids, as well as disclosing "naked" DNA as useful in the claimed methods and compositions as well as a description of compositions by which the claimed antigens may be formulated on page 14, line 15 to page 17, line 4. Furthermore, the specification on page 17, line 5 to page 19, line 20 provides the skilled artisan with a description of how to administer antigens and encoding nucleic acids of the claimed methods and compositions.

Any experimentation that is required to practice the claimed methods is routine. The specification teaches all of the steps required for practicing the proven claimed invention, and all that remains is repetition of these teachings to practice the scope of the claims. In particular, Applicants submit that the patentability of the claimed methods of Group I lies in knowing what to do with the antigens, not in the identification of novel proteins or immunogenic peptides. Moreover, post-filing evidence of record demonstrates that the claimed methods have been carried out according to the teachings of the specification using PSA as an antigen and result in an effective antitumor immune response. Repeating vaccine studies for different antigens, including full-length polypeptides, portions of those polypeptides, and nucleic acids that express the foregoing polypeptides *in situ*, is routine. The routine nature of identifying and using immunogenic peptide is confirmed by each of the experts in the declarations of record. *See* Declaration of Phillip O. Livingston, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996; Declaration of Jean Claude Bystryn, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996, Declaration of Michael Mastrangelo, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996, and Declaration of Robert Oldham, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996. To date, the Examiner has provided no evidence to the contrary nor has there been any indication as to why the declarations of these experts are according no weight. In sum, the claimed inventions of Groups I and II can be easily practiced by a person of ordinary skill in the art without undue experimentation in view of the disclosure in the specification and the knowledge in the art.

C. **The evidence of record definitively demonstrates the operability of the claimed inventions using the guidance provided in the specification.**

The specification as filed provides all the guidance necessary for making and using over represented prostate antigens as tumor vaccines is demonstrated by the objective evidence submitted by Dr. Spitler. *See* Declaration of Lynn E. Spitler, M.D. Pursuant to 37 C.F.R. § 1.132, submitted April 29, 1998. In this declaration, Dr. Spitler attested to the results of five clinical trials using recombinant human PSA, which has been trademarked Onco Vax P™. First, every aspect of the vaccine as used in the clinical trial is disclosed in the specification as filed. The expression system, a baculovirus system, is described at page 6, line 14 to page 7, line 6 and at page 11, lines 5-11 of the specification. Spitler uses one of the species in the claimed genus of over represented antigens on prostate cancer, namely PSA. PSA is disclosed at page 8, line 18 to page 9, line 11. The vaccine composition, *i.e.*, liposomes, is disclosed at page 14, lines 9-23 and at page 16, lines 13-18. The route of administration, *i.e.*, intramuscular, is disclosed at page 16, lines 1-3. The dose (100 μg) and volume (1 ml) administered is disclosed at page 16, lines 19-23. The sequential administration on a monthly basis is disclosed at page 16, lines 24-27 and at page 17, lines 8-12, respectively. Therefore, in every aspect of the clinical trial, Applicants relied on the guidance and examples provided in the specification as filed. Second, the clinical trials using the PSA vaccine was successful, *i.e.*, administration of the vaccine conferred a therapeutic benefit to the patient. Patients in all of the studies demonstrated PSA-specific T cell responses *in vitro* and *in vivo* with the patients in the fifth clinical study demonstrating dramatic and consistent T cell responses. Dr. Spitler's declaration describes the status of the patients in the 5th clinical trial as all having undergone previous treatment, and three of the five patients having metastatic growth in the bone. Notably, in this patient cohort, all five patients evidenced a clinical response to the vaccine. In four of the five patients, the disease stabilized (*i.e.*, did not continue to grow), while one showed improvement (*i.e.*, improved bone scan in patient 2). This is definitive evidence of the *in vivo* operability of the claimed invention.

Appellants submit that the successful use of PSA to obtain clinical relevant responses in a patient cohort that has undergone previous treatment is sufficient to predict to the skilled artisan that other antigens in the class of over represented prostate antigens would elicit similar responses.

The Examiner cites a variety of reasons why protein vaccine efficacy is unpredictable, including proteolytic degradation, failure to reach target area, and potential adverse effects including cross-reactivity with kallikrein family members. *See* Paper No. 33, pages 6 and 8. However, the PSA in the vaccine used by Spitler is a protein. The successful clinical response to the vaccine indicates that PSA was not prematurely degraded, reached the desired target area, and elicited no potential adverse effects such as cross-reactivity with kallikrein family members. To date, the Examiner has provided no scientific rationale or publications that support the assertion that the results obtained using the PSA antigen vaccine is somehow unique and thus inapplicable to other over represented prostate antigens such as PSMA and PAP. In fact, the Examiner continues to argue that PSA will not work as a tumor vaccine. On page 8 of Paper No. 33, the Examiner looks to canine and Dunning rat models, stating that the secreted form of PSA may reduce immunoglobulin responses and/or anergize T cells, result in cross-reactivity to other kallikrein family members, or induce autoimmunity. This argument appears to indicate that the Examiner doubt the evidence of truth or accuracy of the evidence of record and therefore has given the declaration no weight whatsoever. Appellants submit that the Examiner has failed to provide any basis for questioning the validity of the evidence presented by Dr. Spitler. *In re Marzocchi* 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

Reliance on Hodge et al. (*Int. J. Cancer* 63:231-37 (1995)) does not justify the Examiner's failure to give sufficient weight and consideration to the evidence submitted by Dr. Spitler. In fact, continued reliance on Hodge reflects the fundamental lack of understanding of the scientific principles involved in the instant inventions. Hodge discloses the use of a PSA vaccine to elicit an antitumor response in a primate model by administering PSA as a nucleic acid in a recombinant vaccinia virus. Hodge opines regarding the efficacy of the tumor vaccine consists of whole prostate adenocarcinoma cells admixed with adjuvant, stating that little therapeutic benefit has been achieved with such vaccines. *See* Hodge, page 231, column 1. However, as previously stated, cell-based vaccines are fundamentally distinct in operation from protein-based vaccines. First, the whole cell antigen can act as its own antigen presenting cell. As the Office undoubtedly recognizes, the elicitation of immune response using antigen presenting cells that are MHC-mismatched at one or more loci results in a fundamentally different response that can be less antigen specific, of shorter duration, and thus ultimately less effective. The antigen of the claimed methods,

on the other hand, employs self antigen presenting cells, permitting the maximal elicitation of an antigen-specific response. A skilled artisan does not equate cell-based vaccines with purified antigen-based vaccines as demonstrated by the evidence of record. More specifically, Dr. Spitler attested to the use of Hodge by the Examiner, stating:

> I note that The Examiner makes the point several times that previous attempts to actively immunize patients with prostate adenocarcinoma cells admixed with adjuvant have shown little or no therapeutic benefit. However, the use of whole tumor cells is not analogous to the use of recombinant protein such as purified PSA. Whole PSA is not represented on the surface of the tumor cells; thus, the patients would not be expected to be effectively immunized to PSA via this approach. PSA is synthesized within the tumor cells and secreted; therefore, the patients' immune system might be exposed to small amounts of PSA through this approach as some of the tumor cells die and release the internal PSA; these small amounts of antigen would be presented to the immune system in the context of all the other antigens present on and in the tumor cells. This would not be likely to result in an immune response to the PSA. Peptides derived from PSA are present on the surface of the tumor cells, presented in the context of HLA molecules. For these to induce an immune response, it would be expected that they would have to be taken up by the professional antigen presenting cells and represented on the surface of these cells. Again, this would be occurring in the presence of all the other antigens present on and in the tumor cells.
>
> Thus, one cannot take failure of the approaches using whole tumor cells to indicate that immunization with specific antigens will fail (including antigens overrepresented in the prostate gland, an immunologically effective portion thereof, or an antiidiotypic antibody). Indeed, it is the recognition that the use of pure antigens may represent a more effective means of immunization for cancer therapy which has led to intense activity in this field and numerous clinical trials (Spitler, L.E., Engineered Vaccines for Cancer, *Sixth International Congress on Anti-Cancer Treatment* (1995) Paris, February 6-9, 1996; Spitler, L.E., Cancer Vaccines: The Interferon Analogy, *Cancer Biotherapy* (1995) 10:1-3 ....

See Declaration of Lynn E. Spitler Pursuant to 37 C.F.R. § 1.132 submitted November 4, 1996, ¶¶ 2-3 (emphasis added). To date, the Examiner has provided no explanation as to why Hodge continues to be relied upon in view of Dr. Spitler's declaration and the state of the art regarding cell versus protein based vaccines.

Likewise, neither Ezzell (*J. NIH Res.* 7:46-49 (1995)) nor Peshwa et al. (The Prostate 1998) supported the Examiner's assertion of unpredictability. Both Ezzell and Peshwa address the limitations of tumor vaccines using cellular compositions, and therefore are inapplicable to the instant invention. The Examiner states that it is "well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes", citing to Ezzell, again demonstrating a lack of fundamental understanding regarding the scientific principles behind the instant invention. The claimed methods do not employ unique tumor antigens, but rather use antigens that are expressed on both normal and malignant prostate tissue. Thus, the optimism of efficacy for immunotherapy using unique tumor antigens is not relevant to the predictability of the present invention. Similarly, Peshwa employs a cellular vaccine where whole dendritic cells are administered after pulsing the live cells with PSMA peptides, and thus the experimentation required to use such a vaccine is irrelevant to the predictability of the instant invention using antigen vaccines.

Finally, Spitler (*Cancer Biother.* 10:1-3 (1995)) clearly supports the credibility and the predictability of the claimed invention when read in its entirety.

In particular, Spitler states that

> [I]nvestigators working in the university setting using vaccines to treat cancer patients have occasionally seen clinical responses to this therapy, which at times has been dramatic. Almost everyone working in this field has had the experience of seeing a dramatic regression of metastatic disease following vaccine therapy. There are numerous published reports of these responses as well as unpublished observations of individual investigators. (emphasis added)

While Spitler opines regarding the future of tumor vaccines, the Office has selected a single sentence that, in fact, mischaracterizes Spitler's point – that active components of vaccines are identified and purified and are now available for routine vaccine protocols. Hence, when read in its entirety, Spitler does not support the Examiner's contention that the successful use of antitumor vaccines would not be credible to a skilled practitioner or that undue experimentation is required to practice the claimed invention.

Hence, Appellants submit that in the references cited to support the allegations of unpredictability are either scientifically irrelevant or misconstrued, and therefore do not credibly support the Examiner's position. Moreover, to date the Examiner has failed to provide cogent,

scientific reasoning to explain the lack of weight given to Dr. Spitler's declaration. For example, the Examiner has not provided any reference which equates cell-based vaccines with purified protein vaccines. Appellants respectfully note that "[t]he examiner should **never** make the determination [of enablement] based on personal opinion. The determination should always be based on the weight of all of the evidence." MPEP § 2164.05 (emphasis included).

D. The evidence of record definitively demonstrates that the person of skill in the art recognizes the disclosure of PSA as enabling for the genus of over represented antigens and immunologically effective portions thereof.

According to the Brief issued by the Board of Patent Appeals and Interferences entered on January 31, 2001, the Examiner "should take a step back and review the merits of the rejections in light of all the evidence now of record [and] issue an appropriate Office action setting forth the facts and reasoning used to support such a rejection." *See* Paper 28, page 4. To date, the Examiner has not substantively addressed the Declarations submitted by Drs. Livingston, Bystryn, Mastrangelo, and Oldham, particularly with regards to the enablement and predictability of the claimed methods for other over represented prostate antigens like PSA.

Appellants submit that the Declarations of Drs. Livingston, Bystryn, Mastrangelo, and Oldham should be given significant weight because each is a person skilled in the art of tumor vaccines. *See* Declaration of Phillip O. Livingston, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996; Declaration of Jean Claude Bystryn, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996, Declaration of Michael Mastrangelo, M.D. Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996, and Declaration of Robert Oldham Pursuant to 37 C.F.R. § 1.132 submitted November 6, 1996. Collectively, these four individuals represented a total of 86 years of scientific experience and expertise in the field of tumors vaccines resulting in a total of over 500 publications in 1996 (the date of submission of the Declarations). In each case, these skilled artisans reviewed the data in Dr. Spitler's Declaration submitted in 1996 as well as the results from the clinical study. *See* ¶2 of each Declaration. Specifically, each of the declarants attest to the following:

> 5. In my opinion, the results obtained in this clinical study provide evidence that the vaccines are likely to be effective in exerting a

> beneficial effect on patients with prostate tumors or at risk for prostate tumors.[1]
>
> 6. The efficacy shown for the vaccine tested in the foregoing clinical studies further provides evidence that analogous vaccines based on host tissue antigen, such as prostate specific membrane antigen (PSMA) and prostate acid phosphatase (PAP) would behave in a similar manner. It is also known that if the entire antigen is effective as a vaccine, portions of the antigen may be effective as well, especially if manipulated by art-known methods to enhance their immunogenicity, such as by coupling them to carrier.

In other words, four skilled artisans with years of experience and extensive publication records recognized that the results with PSA vaccine were predictive for vaccines using other over represented prostate antigens (or host antigens) as well as for immunologically effective portions thereof. While the Examiner cites two publications using immunologically effective portions of over represented prostate antigens to support his assertion of unpredictability, there is no explanation or reasoning given why there is no weight given to these declarations where skilled artisans attest to the predictability of the identifying immunologically effective portions of these antigens. *See* Paper No. 33, page 9, ¶¶ 2-4. Appellants submit that these declarations strongly support the predictability of using any over represented prostate antigen in the vaccine as disclosed in the instant specification because of the necessary common characteristics shared by these antigens, *i.e.*, substantially unique expression in the prostate. To date, the Examiner has provided no reasoning or valid scientific evidence why these Declarations are unpersuasive.

For all of the reasons stated above, the enablement rejection under 35 U.S.C. § 112, first paragraph may be properly withdrawn.

Issue 3: Claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40 particularly point out and distinctly claim the subject matter that Appellants regards as the invention.

Claims 1-14 and 21-40 were rejected as failing to meet the definiteness requirement. *See* Paper No. 33, pages 10-11. According to the Action, the term "over represented" is a relative term

[1] Appellants note that full text of Dr. Livingston's declaration at paragraph 5 is as follows: In my opinion, the results obtained in this clinical study provide evidence that the vaccines are likely to be effective in exerting a beneficial effect

that renders the claim indefinite because the specification does not provide a standard for ascertaining the relative degree and therefore the skilled artisan would not be reasonably apprised of the metes and bounds of the invention. Appellants assert this rejection is in error.

A. Legal standard of the definiteness requirement.

The definiteness requirement of 35 U.S.C. § 112, second paragraph serves to notify the public of the scope of the patentee's right to exclude as well as to provide a clear measure of what the applicant considers the metes and bounds of the invention. MPEP § 2173. The degree of precision required is one that reasonably apprises the skilled artisan of the scope of the invention and is as precise as the subject matter permits. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 95 (Fed. Cir. 1986), *cert. denied* 480 U.S. 947 (1987) ("The claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matters permits. As a matter of law, no court can demand more."). The use of a relative term fails to automatically render a claim indefinite. MPEP § 2173.05(b). Thus, a relative term or words of degree in a claim are not indefinite if the specification provides a standard for measuring that degree that fully informs one of ordinary skill in the art of the metes and bounds of the claimed invention. *Seattle Box Co., Inc. v. Industrial Crating & Packing, Inc.* 221 U.S.P.Q. 568 (Fed. Cir. 1984), *later appeal* 225 U.S.P.Q. 357 (Fed. Cir. 1985).

B. The specification provides a standard for identifying an antigen as "over represented."

The standard for identifying an antigen as over represented is sufficiently precise that one of ordinary skill in the art would understand the scope of the antigens useful in the claimed methods and compositions. Appellants respectfully submit that the standard for identifying such antigens is plainly defined in the specification at page 9, line 21 to page 10, line 2, disclosing:

> The foregoing list of known antigens which are overrepresented on prostate: prostatic acid phosphatase (PAP); prostate specific antigen (PSA); and prostate specific membrane antigen (PSMA) is offered for the purpose of illustration. These well known antigens (or the epitope bearing

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on patients with prostate tumors or at risk for prostate tumor, though much further work will be required to increase the frequency and potency of the responses.

> fragments thereof) are proteins (or peptides) and are useful in the vaccine of the invention. However, the invention includes any other antigens substantially uniquely present on the prostate gland so that prostate derived tissue can be distinguished from other tissue by virtue of the presence of these antigens." (emphasis added)

First, the skilled artisan would readily understand the scope of the term "over represented antigen" in view of the exemplary antigens provided. At the time of filing, the prior art recognized PAP, PSA, and PSMA as antigens that were essentially prostate-specific. For example, in a medical textbook, it states that "[b]oth prostate-specific antigen [PSA] and prostatic acid phosphatase [PAP] are found by immunohistochemical techniques in normal ... and neoplastic prostatic glandular epithelium." Peterson, *The Urinary Tract and Male Reproductive System* IN 17 PATHOLOGY 928 (Rubin and Farber, eds. 1988). A prior art publication states that "the [PSMA] antigen is expressed exclusively by normal and neoplastic prostate cells and metastases." Israeli et al., *Cancer Res.* 53(3):227-30 (1993). In other words, the prior art recognized each of the disclosed illustrative antigens as prostate-specific, and not cancer specific, antigens at the time of filing.

Second, the specification discloses a standard that readily apprises the skilled artisan of the identity of other antigens that are over represented in the prostate. Quite simply, other useful antigens are those substantially uniquely present on normal prostate tissue to a degree that the prostate derived tissue can be distinguished from other non-prostate tissue by virtue of the presence of these antigens. Such relative terminology is commonplace and readily understood by the skilled artisan, and therefore more precise language is not required. One of skill in the art can readily ascertain the expression of an antigen through a variety of well known and routine techniques that include immunohistochemistry and flow cytometric analysis. Thus, the specification directs the skilled artisan to antigens that are prostate-specific by virtue of an almost exclusive expression on normal prostate tissue. As relative levels of antigen expression is easily determined and routinely used to identify tissues, such disclosure fully informs the skilled artisan of the scope of the antigens that are useful in the claimed methods and compositions.

Because the specification reasonably apprises the skilled artisan of the scope of the invention and is as precise as the subject matter permits, the term "over represented" is sufficiently definite when read in light of the specification. For these reasons , the indefiniteness rejection under 35 U.S.C. § 112, second paragraph may be properly withdrawn.

Issue 4: Claims 1-14 and 21-40 are nonobvious.

Claims 1-14 and 21-40 were rejected as obvious under 35 U.S.C. § 103 (a) over the combination of Spitler (U.S. Patent 5,783,867) in view of Israeli *et al.* (U.S. Patent 5,538,866), Horoszewicz (U.S. Patent 5,162,504), Andriole *et al.* (*Ann. Rev. Med.* 42: 9-15 (1991)) and in view of the art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley *et al.* (*Sem. Surg. Oncol.* 5: 293-301 (1989)). Spitler discloses antitumor vaccine compositions and methods useful for the prevention and treatment of a variety of cancers, using tumor antigens that are associated on multiple tumor types. Israeli discloses a form of passive tumor immunotherapy, *i.e.*, therapeutic agents comprising an antibody directed to PSMA that is conjugated to a cytotoxic agent. Horoszewicz relates to passive immunotherapy using prostate-specific antiidiotypic antibodies. Andriole relates to various forms of treatment for prostate cancer other than immunotherapy. McCarley discloses antibodies against prostate antigens that are useful in passive immunotherapy.

The Office has cited a conglomeration of references that do not teach or suggest (1) active immunotherapy using antigens expressed by normal prostate tissue as in the claims of Group I or (2) vaccine compositions comprising over represented antigens as in the claims of Group II. Therefore, Appellants assert that this rejection is in error.

A. Legal standard of the nonobvious requirement.

A *prima facie* case of obviousness requires the satisfaction of three requirements. First, the combined references must teach or suggest all of the claim limitations. Second, the references must provide a suggestion or motivation to modify the teachings or combine the references either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. Third, the reference must provide a reasonable expectation of success. MPEP § 2143.

More specifically, the obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Critical elements of the invention as a whole which clearly

distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Any disclosure teaching away from the claimed invention also must be considered in the obviousness analysis. MPEP § 2142.01. The fact that an invention can be modified is insufficient to establish *prima facie* obviousness in the absence of a suggestion or motivation to make such a modification. *Id.* Furthermore, if a modification changes the principle of operation of a reference, the teachings of that reference do not render the claimed invention obvious. *Id.* Finally, in the analysis of prior art references, it is improper to exercise hindsight to select bits and pieces from the references to create a motivation to modify that is not found in the references, but only in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Simply stated, the suggestion or motivation to modify a reference must be found in the prior art.

Appellants respectfully submit that a *prima facie* case for obviousness has not been presented. The claimed methods relate to the use of antigens over represented on normal prostate tissue, to induce an active antitumor response in a subject. Therefore, a *prima facie* case of obviousness requires that the cited combination of references result in the use of antigens over represented on normal prostate tissue to induce an active antitumor response in a subject. The combination of cited references must provide a motivation to combine the teachings of these references to result in the claimed methods, and most importantly, the references must provide a reasonable expectation of success in combining these teachings. For the reasons discussed below, the cited references fail to fulfill these requirements for *prima facie* obviousness.

B. The cited references cannot properly be combined to result in the claimed inventions.

Appellants respectfully submit that the combination of the cited references cannot properly be combined to result in the claimed inventions because the references do not teach or suggest the use of over represented prostate antigens in a subject to elicit an active antitumor response or the vaccine compositions comprising over represented prostate antigens. The Examiner seems to rely on two assumptions: (1) the use of cancer-specific antigens to elicit an antitumor response is equivalent to the use of over represented prostate antigens expressed on normal prostate tissue to elicit an antitumor response; and (2) the use of such antigens to generate diagnostic

antibodies and passive immunotherapy reagents is commensurate with the use of such antigens to induce an active antitumor immune response. Appellants submit that neither Spitler, the other cited references, what is known in the art, nor any combination thereof support these assumptions.

1. **Cancer-specific antigens are not equivalent to the use of prostate-specific antigens expressed on normal tissue.**

Appellants respectfully submit that the prior art references nor the knowledge in the art equate cancer-specific antigens with prostate-specific antigens. Spitler fails to teach or suggest the use of over represented prostate antigens to elicit an antitumor response in a subject, a point as yet unappreciated by the Examiner. In its reliance on Spitler, the Office seems to be asserting that antigens associated with the malignant or transformed cell phenotype *per se* are equivalent to over represented prostate antigens that are substantially uniquely on normal prostate tissue as well as on malignant prostate tissue. The claimed methods use antigens that are substantially organ-specific antigens, expressed on both normal and malignant prostate tissue, and thus are not associated with the malignant nature of the prostate cells or other tumor cells *per se*. Spitler, on the other hand, teaches the use of antigens that are associated with the malignant or metastatic nature of the cells. Specifically, Spitler discloses the use of antigens (*i.e.*, CO-029 and GA733-2) that are each characterized by expression on multiple types of malignant cells. *See* Spitler, at column 2, lines 22-26. Thus, the claimed methods are distinct from Spitler in the choice of antigen. Moreover, the antigens selected are characterized as being expressed on a variety of tumors, not any particular tumor or tissue. In other words, Spitler suggests the use of a pan-epitope to stimulate a general antitumor immune response against any malignant cell. Appellants note that some of the antigens cited by Spitler as exemplary antigens can be found at extremely low levels in normal tissue. However, such expression of these antigens in normal tissue does not permit the antigen to be used as a marker that distinguishes that tissue from any other normal tissue. In other words, these antigens are not ones that are substantially uniquely present on a normal tissue to a degree that that tissue can be distinguished from other normal tissue by virtue of the presence of these antigens as in the instant claims. Thus, contrary to the assertions of the Office, Spitler does not teach the use of the over represented prostate antigens in vaccine compositions of Group II or the methods of Group I.

2. **Because active immunotherapy is separate and distinct from passive immunotherapy, there is no motivation to combine Spitler with Israeli, Horoszewicz, and McCarley.**

Presumably because Spitler fails to teach the use of the over represented antigens in the instant claims, the Examiner seeks to combine its teachings with those of Israeli, Horoszewicz, and McCarley. However, there is no suggestion or motivation to combine the cited references because passive and active immunotherapy are recognized in the art as functionally and mechanistically distinct. It is well known that passive and active immunotherapy are distinct and separate biological processes, and therefore the skilled artisan would not consider teachings regarding passive immunotherapy applicable to active immunotherapy. For example, this distinction is recognized in the classic text CANCER: PRINCIPLES & PRACTICE OF ONCOLOGY (De Vita et al., eds. 1993). It states that "[s]trategies for the immunotherapy of cancer can be divided into active and passive approaches." *Id.* at page 305. Active immunotherapy is described as "immunization of the tumor-bearing host with materials designed to elicit an immune reaction capable of eliminating or retarding growth." *Id.* Typically, this involves the development of cellular response to the tumor. Passive immunotherapy, on the other hand, is the administration of exogenous antibodies.[2] *Id.* at Table 17-12. Thus, two critical and undeniable distinctions arise. First, active immunotherapy requires the participation of the host immune response, while passive immunotherapy does not. Thus, antigens that may serve as effective targets for passive immunotherapy may in fact be completely non-immunogenic if the same antigen is administered to the host. Such *in vivo* factors as available antigen presenting cells, suppressive cytokines, lack of appropriate co-stimulatory molecules, and identity as self-antigens can contribute to the lack of immunogenicity of such an antigen to its host's immune system.

Second, it is well recognized that humoral and cellular components of the immune system are not superimposable on each other.

> There is a significant difference in the nature of antigens recognized by humoral and cellular detection systems. Humoral antibodies detect specific epitopes on antigenic molecules, and it is the interaction of these molecules with the variable

[2] Passive immunotherapy can also include the exogenous administration of other immune effectors, such as activated lymphocytes. However, such passive immunotherapy still does not require the active participation of the host immune response.

> region of the antibody that produces recognition. In contrast, antigens recognized by T-cell receptors recognize processed peptides on the surface of the tumor cell or on an antigen presenting cell in conjunction with MHC molecules.

Id. at page 301. Effective active immunotherapy protocols typically elicit a cellular response to the immunizing antigen. Thus, the ability to generate antibodies to PSMA or the suggestion to use such antibodies in passive immunotherapy has no relevance to the instant claims drawn to methods and compositions of active immunotherapy of prostate cancer. These recognized distinctions between active and passive immunotherapy and between antibody and T-cell receptor recognition are still cornerstones of tumor immunotherapy today. Moreover, many of the antibodies disclosed in the cited references are of non-human origin. Therefore, they contain no teaching whatsoever regarding the immunogenicity of the same antigen in humans, a critical element of any active immunotherapy strategy. A person of ordinary skill in the art would not be motivated to combine these references because of these well known distinctions. Therefore, the teachings relating to antibodies in Horoszewicz, McCarley, or Israeli do not provide any motivation to combine these references with Spitler.

For example, Israeli and Horoszewicz disclose prostate antigens, but neither reference teaches nor suggests the use of an antigen to elicit an active antitumor immune response or compositions with such a function. Israeli teaches the use of PSMA in passive immunotherapy of tumors. *See* Israeli, at column 12, line 53 to column 13, line 9. Active immunotherapy is not mentioned. Similarly, Horoszewicz teaches the use of prostate antigen-specific antibodies for passive immunotherapy. Horoszewicz's only disclosure of an active immunotherapy protocol does not employ antigen, but uses anti-idiotype antibodies, a fundamentally different therapy (*i.e.*, antigen administration is never required). *See* Horoszewicz, at column 12, lines 21-29. Because Israeli and Horoszewicz do not teach the use of the prostate antigens in active immunotherapy, neither reference alone or in combination with Spitler teach the instant claimed inventions.

Appellants note that the disclosure of anti-idiotype antibody immunotherapy strategy in Horoszewicz cannot cure the deficiency in Spitler. The use of anti-idiotype antibodies in Horoszewicz provides no teaching or suggestion regarding the use of antigens overexpressed in normal host tissues in active immunotherapy. Anti-idiotype antibodies are distinct from antigen-based therapies in at least three aspects: (1) anti-idiotype antibodies elicit an antitumor response to

a single epitope of the antigen, *i.e.*, the binding cleft of the antibody, whereas antigen administration results in response to multiple epitopes; (2) anti-idiotype antibodies do not require processing and presentation by antigen presenting cells, whereas antigen administration is completely dependent on appropriate processing and presentation by antigen presenting cells; and (3) anti-idiotype antibodies are typically foreign to the host, while the instant prostate antigen is self antigen overexpressed on normal host tissue. The person of ordinary skill in immunology recognizes each of these as significant, distinct, and non-overlapping when considering immunotherapy.

Similarly, McCarley has no teaching or suggestion regarding the use of over represented prostate antigens in active immunotherapy. McCarley's teachings are limited the disclosure of a number of monoclonal antibodies that bind various prostate antigens and may be useful for passive immunotherapy (*e.g.*, when conjugated to a chemotherapeutic agent). Therefore, as with the references above, if these references are to be relevant to the claimed inventions, it must be assumed that the ability to elicit antigen-specific antibodies in non-tumor bearing animals using the disclosed compositions is equivalent to eliciting an effective antitumor response in a subject. Such an assumption cannot be supported scientifically. It is well known in the art the immunogenicity required to elicit specific antibodies that simply bind an antigen does not correlate with, and is often distinct from, the ability to elicit an effective antitumor response, whether humoral or cellular. Moreover, the courts have acknowledge that the ability to induce a response to an antigen, such as an antibody response, is distinct from the ability of an antigen to induce an active or immunoprotective response in a host. *See In re Wright* 27 U.S.P.Q.2d. 1510, 1513 (reasoning that a mere antigenic response is distinct from the induction of active immunity that confer protection against the eliciting agent). Thus, these references do not cure the deficiencies in the Spitler reference.

Finally, Appellants note that Andriole actually teaches away from the need for immunotherapy, as acknowledged by the Examiner in his answer. *See* Paper No. 51, page 7 (stating that Andriole teaches that "surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer.").

Appellants respectfully submit that, in point of fact, Spitler teaches away from the claimed methods and compositions. Spitler teaches the need for a vaccine that is "efficacious in the

prevention and treatment of all cancers." Spitler, at column 1, lines 50-51 (emphasis added). Spitler also teaches that the disclosed compositions are those useful "for the prevention and treatment of a variety of cancers." Spitler, at column 2, lines 19-21 (emphasis added). In other words, Spitler discloses the use of antigens associated with the malignant phenotype *per se*, and not normal tissue, in tumor vaccines. The most preferred antigen being one that is expressed on numerous different types of malignant cells. In order for such a vaccine to be effective and non-toxic, the target antigen would not be one expressed on normal tissue. A skilled artisan would recognize that the administration of a prophylactic vaccine that elicits an immune response to an antigen on normal tissues would result in autoimmunity specific for that tissue, a potentially fatal side effect. Alternatively stated, Spitler's teachings require the use of antigens that are not expressed on normal tissues to achieve its intended purpose. Hence, nothing in Spitler teaches the extension of its teachings to antigens expressed in an organ-specific manner in normal tissues alone or in any combination with the references cited by the Office.

Because the modification of Spitler's teachings to include over represented prostate antigens expressed on normal tissues would render the vaccine unsatisfactory for its intended purpose (*i.e.*, prophylactic and therapeutic vaccine), there is no motivation or suggestion to make such a modification. MPEP § 2143.01 at page 2100-124, second column ("if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification") (citations omitted).

In sum, nothing in Spitler, the other cited references, or the art provide a suggestion or motivation to select over represented prostate antigens, as antigens for active immunotherapy. The other cited references that merely disclose prostate antigens in unrelated contexts do not provide any suggestion or motivation to use these antigens in Spitler's methods.

Finally, the references do not provide a reasonable expectation of success in any combination. The majority of the references do not even address active immunotherapy, thus making it impossible for them to convey any expectation of success regarding the methods or compositions of the instant application.

For the reasons stated above, the rejection under 35 U.S.C. § 103(a) may be properly withdrawn.

Issue 5: Whether the claims are unpatentable under the judicially-created doctrine of obviousness-type double patenting over claims 1-8 of U.S. Patent No. 5,925,362 and over claims 13, 15, 16, and 18-24 of co-pending Application Serial No. 09/300,978.

Claims 1-14 and 21-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent 5,925,362. Claims 1-14 and 21-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 15, 16, and 18-24 of copending application Serial No. 09/300,978.

Signed Terminal Disclaimers are submitted herewith as Exhibit A. Therefore, Applicants respectfully submit that the basis for the rejection may be removed.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

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Respectfully submitted,

By _____

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 08/105,444

1 (Previously presented): A method to induce an antitumor immune response in a potential or actual prostate tumor-bearing subject which method comprises administering to said subject a composition comprising an ingredient which is active to induce said immune response and is selected from the group consisting of

at least one antigen over represented in the prostate gland or an immunologically effective portion thereof; and

an expression system capable of generating *in situ* said antigen.

2 (Previously presented): The method of claim 1 where in said antigen is a protein or peptide.

3 (Previously presented): The method of claim 2 wherein said protein or peptide is selected from the group consisting of prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), prostatic acid phosphatase (PAP) and an immunologically effective portion thereof.

4 (Original): The method of claim 1 wherein said subject is afflicted with metastatic prostate cancer.

5 (Original): The method of claim 1 wherein said subject has been surgically treated to excise said tumor but is at risk for recurrence.

6 (Previously presented): The method of claim 1 wherein said composition is administered to said subject prior to surgical excision of said prostate tumor.

7 (Original): The method of claim 1 wherein said subject is a potential prostate tumor-bearing subject at risk for said tumor.

8 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors in a subject which comprises an ingredient which is active to elicit said immune response, is formulated for parenteral administration and is

an expression system capable of generating *in situ* an antigen over represented on the prostate gland with respect to other tissues or an immunologically effective portion thereof.

9 (Previously presented): The vaccine of claim 8 wherein said antigen is selected from the group consisting of prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), prostatic acid phosphatase (PAP) and an immunologically effective portion thereof.

10 (Original): The vaccine of claim 8 wherein the antigen is encapsulated in a liposome or coupled to a liposome.

11 (Original): The vaccine of claim 10 wherein said liposomes contain an adjuvant or are precipitated with alum.

12 (Original): The vaccine of claim 8 which further includes at least one adjuvant capable of enhancing said antitumor immune response.

13 (Original): The vaccine of claim 12 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria; polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).

14 (Previously presented): The vaccine of claim 8 wherein said expression system consists essentially of DNA encoding said antigen or said portion or wherein said expression system comprises a living expression vector.

15-20 (Canceled)

21 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors in a subject which comprises at least one antigen which is active to elicit said immune response, is formulated for parenteral administration and comprises

said at least one antigen being over represented on the prostate gland with respect to other tissues or an immunologically effective portion thereof,

wherein said antigen is encapsulated in or coupled to a liposome.

22 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors in a subject which comprises at least two ingredients which are active to elicit said immune response and are formulated for parenteral administration, wherein each ingredient is selected from the group consisting of

an antigen over represented on the prostate gland with respect to other tissues or an immunologically effective portion thereof; and

an expression system capable of generating *in situ* said antigen or said portion.

23 (Previously presented): The vaccine of claim 22 wherein said antigen is selected from the group consisting of PSA, PSMA, PAP and an immunologically effective portion thereof.

24 (Original): The vaccine of claim 22 wherein the antigen is encapsulated in a liposome or coupled to a liposome.

25 (Original): The vaccine of claim 24 wherein said liposomes contain an adjuvant or are precipitated with alum.

26 (Original): The vaccine of claim 22 which further includes at least one adjuvant capable of enhancing said antitumor immune response.

27 (Original): The vaccine of claim 26 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria; polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).

28 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors which comprises an ingredient which is active to elicit said immune response, is formulated for parenteral administration, and comprises at least one immunologically effective portion of an antigen over represented on the prostate gland with respect to other tissues said portion being less than the complete antigen.

29 (Previously presented): The vaccine of claim 28 wherein said antigen is selected from the group consisting of prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), prostatic acid phosphatase (PAP).

30 (Previously presented): The vaccine of claim 28 wherein said portion is encapsulated in a liposome or coupled to a liposome.

31 (Original): The vaccine of claim 30 wherein said liposomes contain an adjuvant or are precipitated with alum.

32 (Original): The vaccine of claim 28 which further includes at least one adjuvant capable of enhancing said antitumor immune response.

33 (Original): The vaccine of claim 32 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria; polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).

34 (Previously presented): A pharmaceutical or veterinary vaccine for eliciting an antitumor immune response to prostate tumors in a subject which comprises an ingredient which is active to elicit said immune response, is formulated for parenteral administration, and comprises at least one antigen over represented on the prostate gland with respect to other tissues with the proviso that said antigen is other than human prostate specific antigen (PSA) in a form which is produced in human cells.

35 (Original): The vaccine of claim 34 wherein said antigen is PSA recombinantly produced in nonhuman cells and exhibits posttranslational modifications different from those of PSA produced in human cells.

36 (Previously presented): The vaccine of claim 34 wherein said antigen is selected from the group consisting of PSA, PSMA, PAP and an immunologically effective portion thereof.

37 (Original): The vaccine of claim 34 wherein the antigen is encapsulated in a liposome or coupled to a liposome.

38 (Original): The vaccine of claim 37 wherein said liposomes contain an adjuvant or are precipitated with alum.

39 (Original): The vaccine of claim 34 which further includes at least one adjuvant capable of enhancing said antitumor immune response.

40 (Original): The vaccine of claim 39 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria; polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).